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TITLE OF THE INVENTION

PHARMACEUTICAL COMPOSITIONS

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Respectfully submitted,

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INCORPORATION BY REFERENCE

The content of US application nos. 60/437,516, filed December 30, 2002; and US application no. 60/441,335 filed January 21, 2003 are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to drug-containing compositions, pharmaceutical compositions comprising such drugs, and methods for preparing same.

BACKGROUND OF THE INVENTION

Drugs in pharmaceutical compositions can be prepared in a variety of different forms. Such drugs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such drugs can also be prepared to have different physical forms. For example, the drugs may be amorphous or may have different crystalline polymorphs, perhaps existing in different solvation or hydration states. By varying the form of a drug, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the solvation state of a drug is one of many ways in which to modulate the physical properties thereof.

A solvate may be defined as a compound formed by solvation, for example as a combination of solvent molecules with molecules or ions of a solute. Well known solvent molecules include water, alcohols and other polar organic solvents. Alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and t-butanol. Alcohols also include polymerized alcohols such as polyalkylene glycols (e.g.,

polyethylene glycol, polypropylene glycol). The best-known and preferred solvent is typically water, and solvate compounds formed by solvation with water are termed hydrates.

Propylene glycol (1,2-propylene glycol) is a known substance which is a liquid at ambient temperature. As far as the applicants are aware, propylene glycol is not generally well-known for use in the formation of solvates. US3970651 does disclose the use of propylene glycol in the formation of a crystalline cephalosporin derivative. According to this disclosure a propylene glycolate derivative of a specific cephalosporin zwitterion may be formed in the presence of propylene glycol at acidic pH. This disclosure indicates that the propylene glycol derivative is more stable in solid form than the corresponding ethanolate, especially having excellent colour stability and thermal stability. No other solvates are disclosed in this US patent other than the specific solvate of cephalosporin..

In pharmaceutical formulations certain chemical classes of drugs pose particular problems in preparing pharmaceutical formulations for medical use. One such problem arises in the case of hygroscopic drugs, which tend to absorb water from the air. This is disadvantageous because it makes storage of the drug difficult and can cause degradation of the drug in some cases. Such compounds must be handled in controlled humidity environments during manufacture in order to prevent potency errors due to the changing weight of the drug. The final product must be packaged individual moisture resistant blisters in order to prevent changes in or degradation of the product. Another problem arises from variable hydration states: molecules may change to a more or less stable form as water, a volatile liquid, is lost. Such changes have been known to cause some hydrates to become amorphous. Likewise, absorption of water by a hygroscopic molecule can plasticise the system and lead to recrystallization as a less stable polymorph.

SUMMARY OF THE INVENTION

Solvates of pharmaceutical are rarely used in pharmaceuticals because the solvents are usually volatile thus making it difficult to maintain the solvent in the crystal. If one were to desolvate a pharmaceutical solvate or if it desolvated due to storage conditions or otherwise, it could lead to collapse of the crystal structure, forming an amorphous compound with different physical properties. Obviously, this batch to batch variability and questionable shelf life is undesired. Typically people find solvates of common solvents, such as propanol and ethanol. Propylene glycol is similar in structure to propanol, but is not thought of as a solvent. Propylene glycol solvates of the present invention desolvate only at considerably higher temperatures and harsher conditions than traditional solvates. Propylene glycol solvates are also pharmaceutically acceptable in much larger amounts than we would expose people to with a traditional solvate. Thus, the propylene glycol solvates of the present invention have characteristics that are vastly superior to traditional solvates.

It has now been found that amorphous, crystalline, hygroscopic, or poorly soluble drugs can be made more soluble, stable, and less hygroscopic and can be prepared simply, reliably and inexpensively.

In a first aspect, the present invention provides a pharmaceutical composition comprising a propylene glycol solvate of a drug which is hygroscopic or has low aqueous solubility It has surprisingly been found that by using propylene glycol to form a solvate of a hygroscopic drug, the hygroscopicity of the drug is decreased and/or the stability and aqueous solubility is increased. The drug is therefore much easier to formulate and store than its counterpart untreated or hydrated form.

A number of advantages have been found from the use of propylene glycol in this way. First of all, a higher temperature is required to remove propylene glycol as compared with water or ethanol. This therefore results in an increased thermal stability. Thus the invention further relates to methods of making a an pharmaceutical solvate more stable high temperatures by making a PG solvate of the drug.Secondly, propylene glycol

solvates are generally more pharmaceutically acceptable than other common solvates, including those formed from alcohols other than ethanol. It have further been found that the PG solvates of the present invention have fewer solvation states than hydration states. This is beneficial because production and quality of a drug can be more predictable and consistent.Thus an aspect of the present invention relates to methods of reducing the number of hydration states by making a PG solvate of a drug. PG solvates are also beneficial in addressing the problem with polymorphism. Thus an aspect of the present invention relates to methods of reducing the rate and extent a drug changes form and methods of reducing the chance of making an unwanted form because the PG solvates drives production of a single form. Another aspect of the present invention relates to changing the crystal habit of the drug crystal and preventing a drug crystalline habit to changing to a different habit.

The invention relates to making a pharmaceutical that can be made as a hydrate, more soluble or stable by forming a PG solvate of the drug.

The invention further relates to making a pharmaceutical more stable in a humid environment by making a PG solvate of the drug.

The invention further relates to making a crystalline compound from a pharmaceutical that does not readily crystallize by making a crystalline PG solvate of the drug.

The invention further relates to increasing the solubility of a crystalline pharmaceutical by making a PG solvate of the drug..

The invention further relates to methods of lowing the amount of drug solvation during wet granulation by making a PG solvate of the drug.

A particularly important aspect of the present invention is the realisation that formation of propylene glycol solvates is applicable in a general way to drugs whereby the above

advantages may be conferred. For example, the invention further relates to reducing the level of hygroscopicity of a pharmaceutical metal salt (crystalline, amorphous, solvate (e.g., hydrate)) by forming a PG solvate of the salt. Surprisingly, it has been found that the invention is particularly applicable to those drugs that are in the form of metal salts, such as alkali metal or alkaline earth metal salts. This is especially the case where the metal is selected from sodium, potassium, lithium, calcium and magnesium. Such salts can be hygroscopic and it has hitherto been difficult to find a suitable general means of formulation for these drugs.

Generally, the molar ratio of propylene glycol to drug in the solvate is in the range 0.5 to 2, e.g., 0.5, 1.0, 1.5, 2.0. Depending on the nature of the drug, the ratio of propylene glycol to drug in the solvate may be approximately 0.25, 0.33, 0.5, 0.667, 0.75, 1.0, 1.5, 2.00 or 3.

The composition may further comprise a pharmaceutically-acceptable diluent, excipient or carrier and details of pharmaceutical compositions are also set out in further detail below. The solvate of the pharmaceutical composition according to the present invention is preferably in a crystalline form.

Advantageously, the powder X-ray diffraction spectrum of the composition according to the invention differs from the corresponding powder X-ray diffraction spectrum of unsolvated drug by at least one property selected from:

(i) a loss of at least one peak;

(ii) shifting of more than half the peaks at the 2-theta angle by at least 0.2°, 0.3°, 0.4° or 0.5°; or

(iii) formation of at least one new peak.

It is preferred that the solvate is stable to temperatures of up to 50°C under a stream of nitrogen gas in a thermogravimetric analysis apparatus.

The PXRD could be the same if theis was a host-guest relationship and the PG wasn't completely frozen out. This would be an inclusion compound rather than a true solvate, but it may still be less hygroscopic than a hydrate, less prone to solvent loss than an inclusion with ethanol, less prone to being filled by some toxic co-solvent if PG fits well, and less prone to polymorphism to a less soluble form due to instability caused by a vacated void in the structure. The DSC transitions are likely to occur at different temperatures and have different intensities than for the parent molecule and it's other hydrates/solvates

In one aspect of the invention, the drug is a hygroscopic drug, including hygroscopic metal salts. A non-exhaustive list of hygroscopic drugs is set out in Table 1, along with their suppliers and routes of administration.

Table 1

Product (company)	**Active ingredient**	**Hygroscopic**	**Route(s) of Administration**
Solu-Medrol (P&U)	Methyl prednisolone succinate ester	X	IV
Primaxin IV and IM (Merck)	Imipenem/cilastatin	X (cilastatin)	IV/IM
Vitravene Injection (CIBA)	Fomivirsen sodium	X	IV
Baycol (Bayer)	Cerivastatin sodium	X	Oral
Synercid IV (Aventis)	Dalfopristin/Quinopristin	X	IV
Factrel (Wyeth)	Gonadorelin HCl (decapeptide)	X	IV/SC
Clindets Pledgets (Stiefel)	Clindamycin phosphate (ester prodrug)	X	Topical
Famvir (SKB)	Famciclovir	X	Oral
Nascobal Gel (Schwarz)	Cyanocobalamin	X	

Tasmar (Roche)	Tolcapone	X	Oral
Ellence Injection (P&U)	Epirubicin HCl	X	IV
Colestid (P&U)	Colestipol HCl (anion exc.)	X	Oral
Product (company)	**Active ingredient**	**Hygroscopic**	**Route(s) of Administration**
Pfizerpen Injection (Pfizer)	Penicillin G potassium	X	IV
Bacitracin Injection (Paddock)	Bacitracin (peptide)	X	IV
Lescol (Novartis)	Fluvastatin sodium	X	Oral
Voltaren XR (Novartis)	Diclofenac sodium	X	Oral
Salagen (MGI)	Pilocarpine HCl	X	Oral
Urecholine injection (Merck)	Bethanechol chloride	X	IV
Syprine (Merck)	Trientine 2(HCl)	X	Oral
Singulair chewable (Merck)	Montelukast sodium	X	Oral
Mustargen injection (Merck)	Mechlorethamine HCl	X	IV
Hydrocortone phosphate injection (Merck)	Hydrocortisone phosphate ester	X	IV
Decadron phosphate injection (Merck)	Dexamethasone phosphate ester	X	IV
Gastrocrom (Medeva)	Chromolyn sodium	X	Oral
Mestinon (ICN)	Pyridostigmine bromide	X	Oral
Adipex-P (Gate)	Phentermine HCl	X	Oral
Micardis (Boehringer-Ingelh.)	Telmisartan	X	Oral
Cerubidine injection (Bedford)	Daunorubicin HCl	X	IV
Biltricide (Bayer)	Praziquantel	X	Oral

Elmiron (Alza)	Pentosan polysulfate sodium	X	Oral

In one embodiment, the drug comprises celecoxib. Although the invention is not limited to this particular drug, celecoxib provides a suitable example of the efficacy of the invention. Further details of celecoxib are set out below. In a further embodiment, the drug comprises naproxen, further details of which are also set out below.

In another aspect of the invention, the drug has low aqueous solubility. Typically, low aqueous solubility in the present application refers to a compound having a solubility in water which is less than or equal to 10mg/ml, when measured at 37°C, and preferably less than or equal to 5mg/ml or 1mg/ml. "Low aqueous solubility" can further be defined as less than or equal to 900, 800, 700, 600, 500, 400, 300, 200 150 100, 90, 80, 70, 60, 50, 40, 30, 20 micrograms/ml, or further 10, 5 or 1 micrograms/ml, or further 900, 800, 700, 600, 500, 400, 300, 200 150, 100 90, 80, 70, 60, 50, 40, 30, 20, or 10 ng/ml, or less than 10 ng/ml when measured at 37°C. Aqueous solubility can also be specified as less than 500, 400, 300, 200, 150, 100, 75, 50 or 25 mg/ml. As embodiments of the present invention, solubility can be increased 2, 3, 4, 5, 7, 10, 15, 20, 25, 50, 75, 100, 200, 300, 500, 750, 1000, 5000, or 10,000 times by making a PG solvate of the neutral (crystalline or amorphous), salt, or solvate (e.g., hydrate, ethanolate, methanolate, isopropanaolate, etc.) Further aqueous solubility can be measured in simulated gastric fluid (SGF) rather than water. SGF (non-diluted) of the present invention is made by combining 1 g/L Triton X-100 and 2 g/L NaCl in water and adjusting the pH with 200mM to obtain a solution with a final pH=1.7.

PG solvates of steroids are also included as embodiments of the present invention. Steroids are an important class of drugs which have low aqueous solubility. Particularly important steroids include acetoxypregnenolone, alclometasone dipropionate, aldosterone, anagestone , norethynodrel., androsterone, betamethasone, budesonide,

chlormadinone , chloroprednisone , corticosterone, cortisone, cyclosporine, desogestrel , desoximethasone, desoxycorticosterone, dexamethasone, dichlorisone , dimethisterone, equilenin, equilin, estradiol, estriol, estrogens, estrone, ethisterone, ethynodiol di, ethynyl estradiol, fludrocortisone, fludrocortisone , flunsolide, fluocinolone acetonide, fluorohydrocortisone, fluorometholone, fluoxymesterone, fluprednisolone, flurandrenolide, flurandrenolone, flurogestone , fluticasone propionate, hydrocortisone, hydroxydion, hydroxymethylprogesterone, hydroxyprogesterone, leuprolide , levonorgestrel, loteprednol etabonate, medroxyprogesterone , melengestrol , mesalamine, mestranol, methandrostenolone, methazolamide, methyl testosterone, methylandrostenediol, methylprednisolone, mometasone furoate, norelgestromin , norethandrolone, norethindrone, norethindrone, norethisterone, norgestimate, norgestrel, normethisterone, ondansetron hydrochloride, oxandrolone, oxymetholone, paramethasone, paramethasone , prednisolone, prednisolone , prednisone, pregnenolone, progesterone, prometholone, spironolactone, testosterone, testosterone enanthate, triamcinolone, triamcinolone acetonide, triamcinolone acetonide, vetamethasone disodium phosphate (for some steroids alternative names are included). Formulating steroid drugs presents a problem because of their low aqueous solubility. Embodiments of the present invention are methods of increasing the solubility of steroids by making a PG solvate. Solubility can be specified as discussed above. It is difficult to make crystals of steroids because of their planar structure. Crystallization can be facilitated by making PG solvates. Thus, crystalline PG solvates of steroids and methods of making the same are included in embodiments of the present invention. Steroids generally tend to form non-stoichiometric channel hydrates in which water molecules are trapped in channels between planar steroid regions. Thus, embodiments of the present invention include inhibiting channel formation in steroids by making a PG solvate. Metal salts of steroid drugs can be made and are another example of hygroscopic drugs. Thus, steroid PG solvate are in accordance with one aspect of the present invention. Steroid drugs, whether hygroscopic or not, surprisingly and advantageously form stoichiometric solvates with propylene glycol. Further, the dissolution rate and solubility can be increased with propylene glycol solvates. Thus, the steroid solvates have surprisingly

new properties that make them more favourable for pharmaceutical use and are easier to handle than other forms such as hydrates.

In a further aspect, the present invention provides a method for preparing a propylene glycol solvate of a drug, which method comprises:

(a) contacting propylene glycol with a drug in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) isolating the solvate. (the drug may be, for example, a hygroscopic drug or a drug of low aqueous solubility).

In a further aspect, the present invention provides a method for decreasing the hygroscopicity of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) isolating the solvate, wherein the solvate has decreased hygroscopicity as compared to the drug.

In a further aspect, the present invention provides a method for increasing the aqueous solubility of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) isolatingthe solvate, wherein the solvate has increased aqueous solubility as compared to the drug.

Typically, conditions for making a solvate is the same as for preparing the corresponding non-solvated form of the drug: the solvate of neutral compound would not be pH controlled; the solvate of an acid addition salt would be prepared by including PG with the drug and the acid; and the solvate of a base addition salt would involve adding the drug, the desired base, and the PG. Different co-solvent systems, anti-solvents, or

temperature conditions may be used to encourage PG solvate formation. Seed crystals may be added if they have previously been prepared and isolated.

The step of isolating the solvate may include separating the solution phase from the solvate. Any common method of separation may be employed, including filtration and decanting. The crystalline solvate may be rinsed one or more times with an appropriate solvent following filtration or decanting. The crystalline solvate is preferably dried to remove excess solution phase. Drying may be carried out by thermal processing, vacuum, blowing a stream of gas such as air, nitrogen, argon or another inert gas, or a combination of any or all of these methods. The intention of the rinsing and drying steps is to remove impurities including residual co-solvents and excess PG, acid, or base if used.

The invention will now be described in further detail, by way of example only, with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a differential scanning calorimetry trace of the sodium salt of celecoxib prepared by Example 1 between 50°C and 110°C.

Fig. 2 shows a thermogravimetric analysis of the sodium salt of celecoxib prepared by Example 1, which was conducted from about 30°C to about 160°C.

Fig. 3 shows a powder x-ray diffraction plot of the sodium salt of celecoxib prepared by Example 1.

Fig. 4 shows a differential scanning calorimetry analysis of celecoxib lithium salt MO-116-49B.

Fig. 5 shows a thermogravimetric analysis of celecoxib lithium salt MO-116-49B.

Fig. 6 shows the RAMAN spectrum of celecoxib lithium salt MO-116-49B.

Fig. 7 shows the PXRD spectrum of celecoxib lithium salt MO-116-49B.

Fig. 8 shows a differential scanning calorimetry analysis of celecoxib potassium salt MO-116-49A.

Fig. 9 shows a thermogravimetric analysis of celecoxib potassium salt MO-116-49A.

Fig. 10 shows the RAMAN spectrum of celecoxib potassium salt MO-116-49A.

Fig. 11 shows the PXRD spectrum of celecoxib potassium salt MO-116-49A.

Fig. 12 shows a thermogravimetric analysis of a propylene glycol solvate of a celecoxib sodium salt.

Fig. 13 shows the PXRD spectrum of a propylene glycol solvate of a celecoxib sodium salt.

Fig. 14 shows a thermogravimetric analysis a propylene glycol solvate of a celecoxib potassium salt.

Fig. 15 shows the PXRD spectrum of a propylene glycol solvate of a celecoxib potassium salt.

Fig. 16 shows a thermogravimetric analysis of a propylene glycol solvate of a celecoxib lithium salt.

Fig. 17 shows the PXRD spectrum of a propylene glycol solvate of Naproxen sodium salt.

Fig. 18 shows a thermogravimetric analysis of a propylene glycol solvate of Naproxen sodium salt.

Fig. 19A shows the PXRD spectrum of celecoxib free acid. Fig. 19B shows the RAMAN spectrum of celecoxib free acid.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to propylene glycol solvate forms, preferably stoichiometric, of certain drugs, including those which are hygroscopic or which have low aqueous solubility. Whilst the invention is applicable to any such drugs in general, metal salts of the non-steroidal antinflammatory drug celecoxib serve to illustrate the present invention by way of example. Unlike traditional non-steroidal antinflammatory drugs (NSAIDs), celecoxib is a selective inhibitor of cyclooxygenase II (COX-2) which causes fewer side effects when administered to a subject. The present applicants have identified new forms of celecoxib that have improved properties, particularly as oral

formulations. The applicants have found that a stable, crystalline sodium salt of celecoxib can be synthesised which is significantly more soluble in water than the neutral celecoxib on the market. This sodium salt, or other metal salts can subsequently be improved according to the present invention by the production of a propylene glycol solvate thereof.

Salts of celecoxib are formed by reaction of celecoxib with an acceptable base. Acceptable bases include, but are not limited to, metal hydroxides and alkoxides with sufficiently high pK_a=s (e.g., pK_a=s greater than about 11 to about 12).
The celecoxib salt can be characterized by differential scanning calorimetry (DSC). The sodium salt of celecoxib prepared in (Comparative) Example 1 is characterized by at least 3 overlapping endothermic transitions between 50°C and 110°C (Fig. 1). Conditions for DSC can be found in Example 1.

Celecoxib salts can be characterized by thermogravimetric analysis (TGA). The sodium salt of celecoxib prepared by Example 1 was characterized by TGA, and had about 3 loosely bound equivalents of water that evaporated between about 30°C and about 40°C, one more tightly bound equivalent of water that evaporated between about 40°C and about 100°C, and one very tightly bound equivalent of water that evaporated between about 140°C and about 160°C (Fig. 2). Conditions for TGA can be found in Example 1.

Celecoxib salts can also be characterized by powder x-ray diffraction (PXRD). The sodium salt of celecoxib prepared by Example 1 had an intense reflection or peak at a 2-theta angle of 6.40°, and other reflections or peaks at 7.01°, 16.73°, and 20.93° (Fig. 3). Conditions for PXRD can be found in Example 1.

Further celecoxib salts are characterized in the Examples below.

Naproxen is a further drug which may be used to illustrate the present invention. Naproxen is a member of the ibufenac group of NSAIDs. This drug is practically insoluble in water.

An aspect of the present invention provides a pharmaceutical composition comprising a propylene glycol solvate of a drug that is less hygroscopic than the amorphorous, neutral crystalline, or salt crystalline form, or has low aqueous solubility Hygroscopicity should be assessed by dynamic vapor sorption analysis, in which 5-50 mg of the compound is suspended from a Cahn microbalance. The compound being analyzed should be placed in a non-hygroscopic pan and its weight should be measured relative to an empty pan composed of identical material and having nearly identical size, shape, and weight. Ideally, platinum pans should be used. The pans should be suspended in a chamber through which a gas, such as air or nitrogen, having a controlled and known percent relative humidity (%RH) is flowed until eqilibrium criteria are met. Typical equilibrium criteria include weight changes of less than 0.01 % change over 3 minutes at constant humidity and temperature. The relative humidity should be measured for samples dried under dry nitrogen to constant weight (<0.01 % change in 3 minutes) at 40oC unless doing so would de-solvate or otherwise convert the material to an amorphous compound. In one aspect, the hygroscopicity of a dried compound can be assessed by increasing the RH from 5 to 95 % in increments of 5 % RH and then decreasing the RH from 95 to 5 % in 5 % increments to generate a moisture sorption isotherm. The sample weight should be allowed to equilibrate between each change in %RH. If the compound deliquesces or becomes amorphous between above 75 % RH, but below 95 % RH, the experiment should be repeated with a fresh sample and the relative humidity range for the cycling should be narrowed to 5-75 % RH or 10-75 % RH instead of 5-95 %RH. If the sample cannot be dried prior to testing due to lack of form stability, than the sample should be studied using two complete humidity cycles of either 10-75 % RH or 5-95 % RH, and the results of the second cycle should be used if there is significant weight loss at the end of the first cycle.

Hygroscopicity can be defined using various parameters. For purposes of the present invention, a non-hygroscopic molecule should not gain or lose more than 1.0%, or more preferably, 0.5 % weight at 25 °C when cycled between 10 and 75 % RH (relative humidity at 25 °C). The non-hygroscopic molecule more preferably should not gain or lose more than 1.0%, or more preferably, 0.5 % weight when cycled between 5 and 95 %RH at 25 °C, or more than 0.25 % of its weight between 10 and 75 % RH. Most preferably, a non-hygroscopic molecule will not gain or lose more than 0.25 % of its weight when cycled between 5 and 95 % RH.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of Callaghan et al., *Equilibrium moisture content of pharmaceutical excipients*, in Drug Dev. Ind. Pharm., Vol. 8, pp. 335-369 (1982). Callaghan et al. classified the degree of hygroscopicity into four classes.

Class 1: Non-hygroscopic	Essentially no moisture increases occur at relative humidities below 90%.
Class 2: Slightly hygroscopic	Essentially no moisture increases occur at relative humidities below 80%.
Class 3: Moderately hygroscopic	Moisture content does not increase more than 5% after storage for 1 week at relative humidities below 60%.

Class 4: Very hygroscopic Moisture content increase may occur at relative humidities as low as 40 to 50%.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of the European Pharmacopoeia Technical Guide (1999, p. 86) which has

defined hygrospocity, based on the static method, after storage at 25°C for 24 h at 80 percent RH:

Slightly hygroscopic: Increase in mass is less than 2 percent m/m and equal to or greater than 0.2 percent m/m.

Hygroscopic: Increase in mass is less than 15 percent m/m and equal to or greater than 0.2 percent m/m.

Very Hygroscopic: Increase in mass is equal to or greater than 15 percent m/m.

Deliquescent: Sufficient water is absorbed to form a liquid.

PG solvates of the present invention can be set forth as being in Class 1, Class 2, or Class 3, or as being Slightly hygroscopic, Hygroscopic, or Very Hygroscopic. PG solvates of the present invention can also be set forth based on their ability to reduce hygroscopicity. Thus, preferred PG solvates of the present invention are less hygroscopic than the non-PG solvated reference compound, e.g., the reference compound of a celecoxib sodium salt PG solvate is celecoxib sodium salt. Further included in the present invention are PG solvates that do not gain or lose more than 1.0% weight at 25 °C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 1.0% weight under the same conditions. Further included in the present invention are PG solvates that do not gain or lose more than 0.5% weight at 25 °C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 0.5% or more than 1.0% weight under the same conditions. Further included in the present invention are PG solvates that do not gain or lose more than 1.0% weight at 25 °C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 1.0% weight under the same conditions. Further included in the present invention are PG solvates that do not gain or lose more than 0.5% weight at 25 °C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5% or more than 1.0%

weight under the same conditions. Further included in the present invention are PG solvates that do not gain or lose more than 0.25% weight at 25 °C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5% or more than 1.0% weight under the same conditions.

Further included in the present invention are PG solvates that have a hygroscopicity (according to Callaghan et al.) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Non-limiting examples include; a Class 1 PG solvate of a Class 2 reference compound, a Class 2 PG solvate of a Class 3 reference compound, a Class 3 PG solvate of a Class 4 reference compound, a Class 1 PG solvate of a Class 3 reference compound, a Class 1 PG solvate of a Class 4 reference compound, or a Class 2 PG solvate of a Class 4 reference compound.

Further included in the present invention are PG solvates that have a hygroscopicity (according to the European Pharmacopoeia Technical Guide) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Non-limiting examples include; a Slightly hygroscopic PG solvate of a Hygroscopic reference compound, a Hygroscopic PG solvate of a Very Hygroscopic reference compound, a Very Hygroscopic PG solvate of a Deliquescent reference compound, a Slightly hygroscopic PG solvate of a Very Hygroscopic reference compound, a Slightly hygroscopic PG solvate of a Deliquescent reference compound, a Hygroscopic PG solvate of a Deliquescent reference compound.

The compositions of the present invention, including the active pharmaceutical ingredient (api) and formulations comprising the api, are suitably stable for pharmaceutical use. Preferably, the api or formulations thereof of the present invention are stable such that when stored at 30 deg. C for 2 years, less than 0.2% of any one degradant is formed. The term degradant refers herein to product(s) of a single type of chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the

purpose of the present invention, it would be considered a single degradant. More preferably, when stored at 40 deg. C for 2 years, less than 0.2% of any one degradant is formed. Alternatively, when stored at 30 deg. C for 3 months, less than 0.2% or 0.15%, or 0.1% of any one degradant is formed, or when stored at 40 deg. C for 3 months, less than 0.2% or 0.15%, or 0.1% of any one degradant is formed. Further alternatively, when stored at 60 deg. C for 4 weeks, less than 0.2% or 0.15%, or 0.1% of any one degradant is formed. The relative humidity (RH) may be specified as ambient (RH), 75% (RH), or as any single integer between 1 to 99%

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with a drug or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of celecoxib per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, a liquid, or any other form reasonably adapted for such administration. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the drug, such as tablets or capsules.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents;

confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination, are preferred diluents. These diluents are chemically compatible with celecoxib. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of celecoxib, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colocorn™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose,

methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also prevent or inhibit crystallization or recrystallization of a celecoxib salt of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates;

HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients.
Non-limiting examples of surfactants that can be used as wetting agents in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol

laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the celecoxib in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of the drug, such as celecoxib, from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of

therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid), malic acid, maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize metal salts of drugs like celecoxib typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending a celecoxib salt of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending a drug salt such as a celecoxib salt of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a dry granulation step. A salt of the present invention is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5

micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents are preferably added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in drug content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein a celecoxib salt is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Celecoxib dosage forms of the invention preferably comprise celecoxib in a daily dosage amount of about 10 mg to about 1000 mg, more preferably about 25 mg to about 400 mg, and most preferably about 50 mg to about 200 mg.

EXEMPLIFICATION

Below are standard procedures for acquiring Raman, XRD, DSC and TGA data herein. These procedures were followed for each respective method of analysis herein unless otherwise indicated. Any contradictory information in an Example controls.

Procedure for Raman Acquisition, Filtering and Binning

Acquisition

The sample was either left in the glass vial in which it was processed or an aliquot of the sample was transferred to a glass slide. The glass vial or slide was positioned in the sample chamber. The measurement was made using an Almega™ Dispersive Raman (Almega™ Dispersive Raman, Thermo-Nicolet, 5225 Verona Road, Madison, WI 53711-4495) system fitted with a 785nm laser source. The sample was manually brought into focus using the microscope portion of the apparatus with a 10x power objective (unless otherwise noted), thus directing the laser onto the surface of the sample. The spectrum was acquired using the parameters outlined in Table 1. (Exposure times and number of exposures may vary; changes to parameters will be indicated for each acquisition.)

Filtering and Binning

Each spectrum in a set was filtered using a matched filter of feature size 25 to remove background signals, including glass contributions and sample fluorescence. This is particularly important as large background signal or fluorescence limit the ability to accurately pick and assign peak positions in the subsequent steps of the binning process. Filtered spectra were binned using the peak pick and bin algorithm with the parameters given in Table 2. The sorted cluster diagrams for each sample set and the corresponding cluster assignments for each spectral file were used to identify groups of samples with similar spectra, which was used to identify samples for secondary analyses.

Table 1. Raman Spectral acquisition parameters

Parameter	Setting Used
Exposure time (s)	2.0
Number of exposures	10
Laser source wavelength (nm)	785
Laser power (%)	100
Aperture shape	pin hole
Aperture size (um)	100
Spectral range	104-3428
Grating position	Single
Temperature at acquisition (°C)	24.0

Table 2. Raman Filtering and Binning Parameters

Parameter	Setting Used
Filtering Parameters	
Filter type	Matched
Filter size	25
QC Parameters	
Peak Height Threshold	1000
Region for noise test (cm^{-1})	0-10000
RMS noise threshold	10000
Automatically eliminate failed spectra	Yes

Region of Interest	
Include (cm^{-1})	104-3428
Exclude region I (cm^{-1})	
Exclude region II (cm^{-1})	
Exclude region III (cm^{-1})	
Exclude region IV (cm^{-1})	
Peak Pick Parameters	
Peak Pick Sensitivity	Variable
Peak Pick Threshold	100
Peak Comparison Parameters	
Peak Window (cm^{-1})	2
Analysis Parameters	
Number of clusters	Variable

Procedure for X-Ray Powder Diffraction

All x-ray powder diffraction patterns were obtained using the D/Max Rapid X-ray Diffractometer (D/Max Rapid, Contact Rigaku/MSC, 9009 New Trails Drive, The Woodlands, Texas, USA 77381-5209) equipped with a copper source (Cu/K_α 1.5406Å), manual x-y stage, and 0.3mm collimator. The sample was loaded into a 0.3mm boron rich glass capillary tube (e.g., Charles Supper Company, 15 Tech Circle, Natick Massachusetts 01760-1024) by sectioning off one end of the tube and tapping the open, sectioned end into a bed of the powdered sample or into the sediment of a slurried precipitate. Note, precipitate can be amorphous or crystalline. The loaded capillary was mounted in a holder that was secured into the x-y stage. A diffractogram was acquired (e.g., Control software: RINT Rapid Control Software, Rigaku Rapid/XRD, version

1.0.0, © 1999 Rigaku Co.) under ambient conditions at a power setting of 46kV at 40mA in reflection mode, while oscillating about the omega-axis from 0 - 5 degrees at 1 degree/s and spinning about the phi-axis at 2 degrees/s. The exposure time was 15 minutes unless otherwise specified. The diffractogram obtained was integrated over 2-theta from 2–60 degrees and chi (1 segment) from 0-360 degrees at a step size of 0.02 degrees using the *cyllnt* utility in the RINT Rapid display software (Analysis software: RINT Rapid display software, version 1.18, Rigaku/MSC.) provided by Rigaku with the instrument. The dark counts value was set to 8 as per the system calibration (System set-up and calibration by Rigaku); normalization was set to average; the omega offset was set to 180°; and no chi or phi offsets were used for the integration. The analysis software JADE XRD Pattern Processing, versions 5.0 and 6.0 ((8)1995-2002, Materials Data, Inc. was also used.

Procedure for Differential Thermal Analysis (DSC)

An aliquot of the sample was weighed into an aluminum sample pan. (e.g., Pan part # 900786.091; lid part # 900779.901; TA Instruments, 109 Lukens Drive, New Castle, DE 19720) The sample pan was sealed either by crimping for dry samples or press fitting for wet samples (e.g., hydrated or solvated samples). The sample pan was loaded in to the apparatus (DSC: Q1000 Differential Scanning Calorimeter, TA Instruments, 109 Lukens Drive, New Castle, DE 19720), which is equipped with an autosampler, and a thermogram was obtained by individually heating the sample (e.g., Control software: Advantage for QW- Series, version 1.0.0.78, Thermal Advantage Release 2.0, © 2001 TA instruments – Water LLC) at a rate of 10°C /min from T_{min} (typically 20°C) to T_{max} (typically 300°C) (Heating rate and temperature range may vary, changes to these parameters will be indicated for each sample) using an empty aluminum pan as a reference. Dry nitrogen (e.g., Compressed nitrogen, grade 4.8, BOC Gases, 575 Mountain Avenue, Murray Hill, NJ 07974-2082) was used as a sample purge gas and was set at a flow rate of 50 ml/min. Thermal transitions were viewed and analyzed using the analysis software (Analysis Software: Universal Analysis 2000 for Windows

95/95/2000/NT, version 3.1E; Build 3.1.0.40, © 1991 - 2001TA instruments – Water LLC) provided with the instrument.

Procedure for Thermogravimetric Analysis (TGA)

An aliquot of the sample was transferred into a platinum sample pan. (Pan part # 952019.906; TA Instruments, 109 Lukens Drive, New Castle, DE 19720) The pan was placed on the loading platform and was then automatically loaded in to the apparatus (TGA: Q500 Thermogravimetric Analyzer, TA Instruments, 109 Lukens Drive, New Castle, DE 19720) using the control software (Control software: Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0, © 2001 TA instruments – Water LLC). Thermograms were obtained by individually heating the sample at 10°C /min from 25°C to 300°C (Heating rate and temperature range may vary, changes in parameters will be indicated for each sample) under flowing dry nitrogen (e.g., Compressed nitrogen, grade 4.8, BOC Gases, 575 Mountain Avenue, Murray Hill, NJ 07974-2082), with a sample purge flow rate of 60ml/min and a balance purge flow rate of 40ml/min. Thermal transitions (e.g. weight changes) were viewed and analyzed using the analysis software (Analysis Software: Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E; Build 3.1.0.40, © 1991 - 2001TA instruments – Water LLC) provided with the instrument.

Example 1 (Comparative)

Celecoxib sodium salt from aqueous solution

To 77.3 mg of commercially-available celecoxib was added 1.0 mL distilled water, followed by 0.220 mL of 1 M NaOH (VWR). The mixture was heated with stirring to 60°C, whereupon an additional 1.0 mL distilled water was added. Solid NaOH (22 mg) was added, and the solid NaOH and celecoxib dissolved. The mixture was heated again at 60°C to evaporate water. About 15 mL reagent-grade ethanol was added, while the mixture was stirred and heated at 60°C with air blowing over the solution. Heating

continued until the solution was dry. The resulting material was analyzed by powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), the results of which are seen in Figs. 1-3. The product was found to contain about 5.5 equivalents of water per equivalent of salt.

DSC analysis of the salt sample prepared above was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (^{8}2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (^{8}2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing 2.594 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was 20°C with a heating rate of 10°C/minute, and the ending temperature was 200°C. The resulting DSC analysis is shown in Fig. 1.

TGA analysis of the salt sample prepared above was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (^{8}2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (^{8}2001 TA Instruments-Water LLC).

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA of the sample was performed by placing 2.460 mg of sample in a platinum pan. The starting temperature was 20°C with a heating rate of 10degreesC/minute, and the ending temperature was 300°C. The resulting TGA analysis is shown in Fig. 2.

A powder X-ray diffraction pattern for the salt sample prepared above was performed using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control Software, Rigaku Rapid/XRD, version 1.0.0 (©1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ((©1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a K line at 1.5406Å; x-y stage was manual; collimator size was 0.3 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 mm collimator; the collection time was 60 minutes; the temperature was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

The PXRD pattern for the compound prepared above is shown in Fig. 3. In the diffractogram of Fig. 3, the background has been removed.

Example 2 (Comparative)

Celecoxib-Lithium Salt Preparation Method: MO-116-49B

To 100mg of commercially available Celecoxib was added 0.35M LiOH(aq) (Lithium Hydroxide Monohydrate – Aldrich Cat#25,427-4, Lot 00331K1) solution with a Lithium:celecoxib ratio of 1.53:1 in a vial with a Teflon coated silicon rubber septum cap. The mixture was gently heated during dissolution with occasional swirling until all solids dissolved. Flowing dry nitrogen was blown over the solution for 2 days through stainless steel needles inserted into the septum cap until the solution was dry. Characterization of the product was achieved via DSC (Fig. 4), TGA (Fig. 5), Raman spectroscopy (Fig. 6) and PXRD (Fig. 7).

Unless specifically stated, all equipment and instrumentation used for analysis is the same as in Example 1.

Celecoxib-Lithium Salt Data (DSC)

1.56mg of collected sample was placed into an aluminum DSC pan with cover. The DSC pan was sealed with crimping and placed in TA Instruments Q1000 DSC. The sealed pan was heated 10°C/min to 300°C with 50ml/min nitrogen purge gas. Figure 4 is the resulting DSC analysis.

Celecoxib-Lithium Salt Data (TGA)

8.2290mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA. The pan was heated 10°C/min to 300°C with 40ml/min nitrogen purge gas. The results of the TGA are depicted in Fig. 5.

Celecoxib-Lithium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 μm slit
	Sample position: Microscope
	Camera temperature: -50 C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

The results of the Raman spectroscopy are depicited in Fig. 6.

Celecoxib-Lithium Salt Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube.. The tube was placed into a Rigaku D/Max Rapid PXRD and set to: Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes.

Example 3 (Comparative)

Celecoxib-Potassium Salt: Preparation Method MO-116-49A

100mg of Celecoxib (Fako Ilaclari A,S,) was dissolved in a 0.35M KOH(aq) solution (Potassium Hydroxide – Spectrum, Cat# P0180, Lot#PN0690) with a Potassium:Celecoxib ratio of 1.40:1 in a vial with a Teflon coated silicon rubber septum cap. The resulting solution was gently warmed during dissolution with occasional

swirling until all solids dissolved. After all solids were dissolved, the solution was dried by flowing dry nitrogen over the solution for 2 days through stainless steel needles inserted into the septum cap. Analysis of the resulting product was performed. Characterization of the product was achieved via DSC (Fig. 8,) TGA (Fig. 9), Raman spectroscopy (Fig. 10) and PXRD (Fig. 11).

Celecoxib-Potassium Salt (MO-116-49A) Data (DSC)

1.119 mg of collected sample was placed into an aluminum DSC pan with cover. The pan was sealed with crimping and placed into a TA Instruments Q1000 DSC. The DSC was heated 10°C/min to 300°C with 50ml/min nitrogen purge gas. The results are depicted in the graph of Fig. 8.

Celecoxib-Potassium Salt (MO-116-49A) Data (TGA)

5.9890 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated10°C/min to 90°C, held for 10 minutes, ramped 10°C/min to 300°C, and held for 10 minutes with 40ml/min nitrogen purge gas. The results are depicted in Fig. 9:

Celecoxib-Potassium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collections. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 μm slit
	Sample position: Microscope
	Camera temperature: -50 C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

The results are depicted in Fig. 10.

Celecoxib-Potassium Salt (MO-116-49A) Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The results are depicted in Fig. 11.

Example 4

A propylene glycol solvates of the sodium salt of celecoxib was prepared. To a solution of celecoxib (312 mg; 0.818 mmol) in Et_2O (6 mL) was added propylene glycol (0.127 ml, 1.73 mmol). To the clear solution was added NaOEt in EtOH (21%, 0.275 µL, 0.817 mmol). After 1 minute, crystals began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The off-white solid was then air-dried and collected. This was a 1:1 solvate.

The solid was characterized by TGA and PXRD. The results are depicted in Fig. 12 and 13.

Example 5

A propylene glycol solvate of the potassium salt of celecoxib was prepared. To a solution of celecoxib (253 mg, 0.664 mmol) in Et_2O (6 mL) was added propylene glycol (0.075 ml, 1.02 mmol). To the clear solution was added KOtBu in THF (1 M, 0.66 mL, 0.66 mmol). Crystals immediately began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. This solid was a 1:1 solvate. The solid was characterized by TGA and PXRD. The results are depicted in Fig. 14 and 15.

Example 6

A propylene glycol solvate of lithium salt of celecoxib was prepared. To a solution of celecoxib (264 mg, 0.693 mmol) in Et_2O (8 mL) was added propylene glycol (0.075 ml, 1.02 mmol). To the clear solution was added tBu-Li in pentane (1.7 M, 0.40 mL, 0.68 mmol). A brown solid formed immediately but dissolved within one minute yielding white solid. The white solid crystallized completely after 10 minutes. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. The solid was a 1:1 solvate. The solid was characterized by TGA and the results are depicted in Fig. 16.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

Example 7

A propylene glycol solvate of a sodium salt of Naproxen was prepared. To a solution of Naproxen (mg, mmol) in Et_2O (10 mL) was added propylene glycol (ml, mmol). To the

clear solution was added NaOEt in EtOH (21%, mL, mmol). The solution became slightly yellow due to NaOEt. After 1 minute, crystals begin to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The product was then air-dried and collected. The solvate was 2:1 Naproxen Na:PG. The solid was characterised by TGA and PXRD. The results are depicted in Fig. 17 and Fig. 18.

Example 8

Preparation of Celecoxib Sodium

The free acid of Celecoxib (5.027 g) was suspended in an aqueous solution of NaOH (13.181 mL, 1 M). The suspension was gently heated at 60°C for 1 minute to dissolve the remaining solid. The mixture was allowed to cool to room temperature, which yielded no precipitation. Further cooling in an ice bath for 1 hour gives precipitation of the product. The resulting solution was filtered and allowed to air dry.

Characterization of the product has been achieved via TGA, DSC, PXRD, Raman spectroscopy, microscopy, and ^1H NMR spectroscopy. NMR acquisitions were performed on a Varian 300 MHz Spectrometer in (methyl sulfoxide)-d^6.

The PXRD pattern has characteristic peaks as shown in Fig. 19A. An intense peak can be seen at 19.85 with other peaks at 2-theta angles including but not limited to, 3.57, 10.69, 13.69, 20.43, and 21.53. The crystal can be characterized by any one, any two, any three, any four, or all five of the peaks above, or any one or combination of 2-theta angles of Fig. 19A.

Results of Raman spectroscopy can be seen in Fig. 19B. Raman shift (cm^{-1}) peaks occur at positions including, but not limited to, any two, any three, any four, all five of 1617.11, 1446.20, 1373.73, 975.02 and 800.15, or any combinations 2, 3, 4, 5 or more peaks of Fig. 19B.

Example 9

Preparation of Olanzapine PG solvate

Olanzapine PG solvate was prepared by dissolving 1.05 g of olanzapine form I in 8 ml of isopropylacetate and 2.0 ml of propylene glycol with heating. The hot liquid was filtered through an 0.2 um nylon syringe filter. Crystallization occurred after cooling to RT. The addition of a small amount of seed crystals from a previous reaction followed by sonnicated for 10 seconds also facilitated crystallization. The product was isolated by suction filtration, rinsed with iso-propylacetate and allowed to air dry.

Product is a fine yellow powder. The crystals grow in three dimensions yielding chunks.

Another batch of olanzapine PG solvate was prepared by dissolving 16.2 mg of olanzapine form I in 0.05 ml of PG and 0.05 ml of iso-propylacetate with heating. The sample was cooled to RT and a single crystal from a previous preparation was added. The sample was allowed to sit undisturbed for 2 days during which an aggregate clump of several large crystals grew. The contents of the vial were poured onto filter paper. The crystals were transferred to a filter paper, rinsed with a single drop of IPAC, and dried by dabbing with the filter paper. The rinse procedure was repeated a total of four times with fresh filter paper. Characterization of the product has been achieved via TGA, DSC, PXRD, Raman spectroscopy, and microscopy.

The PXRD pattern has characteristic peaks as shown for two sample preparations in Fig. 20A and 20B. Peaks can be seen at 2-theta angles including but not limited to 8.330, 8.949, 11.749, 14.470, 15.610, 17.950, 19.209, 19.570, 20.649, 21.410, 22.030, and 23.590 in Fig. 20A. The crystal can be characterized by any one, any two, any three, any four, any 5, any 6, any 7, any 8, any 9, any 10, any 11 (each combination included as individual species of the present invention), or all 12 of the peaks above. In the second representative sample, peaks can be seen at 2-theta angles including buy not limited to 8.390, 8.889, 13.951, 14.450, 15.550, 17.911, 19.130, 19.550, 20.610, 21.469, 22.070, and 23.310 in Fig. 20A. The crystal can be characterized by any one, any two, any three, any four, any 5, any 6, any 7, any 8, any 9, any 10, any 11 (each combination included as individual species of the present invention), or all 12 of the peaks above.

Results from TGA analysis show an 18.05% weight loss representing loss of PG (Fig. 21). Results from DSC show a melting temperature for the solvate as 92.63 deg C (Fig. 22).

CLAIMS:

1. A pharmaceutical composition comprising a propylene glycol solvate of a drug which is hygroscopic or which has low aqueous solubility.

2. A composition according to claim 1, wherein the mole ratio of propylene glycol to drug in the solvate is in the range 0.25 to 2.

3. A composition according to claim 1, wherein the solvate is in a crystalline form.

4. A composition according to claim 3, having a powder X-ray diffraction spectrum which differs from the corresponding powder X-ray diffraction spectrum of the unsolvated drug by at least one property selected from

(i) a loss of at least one peak;

(ii) shifting of more than half the peaks at the 2-theta angle by at least 0.3°; and

(iii) formation of at least one new peak.

5. A composition according to claim 1, wherein the solvate is stable to temperatures of up to 50°C under a stream of gas in a thermogravimetric analysis apparatus.

6. A composition according to claim 1, wherein the drug is in the form of a metal salt.

7. A composition according to claim 6, wherein the metal is an alkali metal or an alkaline earth metal.

8. A composition according to claim 7, wherein the metal is selected from Na, K, Li, Ca and Mg.

9. A composition according to claim 1, wherein the drug is selected from the group of hygroscopic drugs consisting of Celecoxib, Naproxen, Methyl prednisolone succinate ester, Impinem/Cilastatin, Fomivirsen sodium, Cerivastatin sodium, Dalfopristin/Quinopristin, Gonadorelin HCl(decapeptide), Clindamycin phosphate (ester prodrug), Famciclovir, Cyanocobalamin, Tolcapone, Epirubicin HCl, Colestipol HCl (anion exc.), Penicillin G potassium, Bacitracin (peptide), Fluvastatin sodium, Diclofenac sodium, Pilocarpine HCl, Bethanechol chloride, Trientine 2 (CHl), Montelukast sodium, Mechlorethamine HCl, Hydrocortisone phosphate ester, Dexamethasone phosphate ester, Chromolyn sodium, Pyridostigmine bromide, Phentermine HCl, Telmisartan, Daunorubicin HCl, Praziquantel, and Pentosan polysulfate sodium.

10. A composition according to claim 1, wherein the drug has low aqueous solubility and is selected from the group consisting of steroid drugs.

11. A composition according to claim 1, which further comprises a pharmaceutically-acceptable diluent, excipient or carrier.

12. A propylene glycol solvate of a sodium salt of celecoxib, which has peaks at 2-theta angles of approximately 3.8°, 7.6°, 8.2°, 11.3° and 20.6°, in a powder X-ray diffraction spectrum.

13. A propylene glycol solvate of a potassium salt of celecoxib, which has peaks at 2-theta angles of approximately 3.8°, 7.5°, 11.3° and 18.3°, in a powder X-ray diffraction spectrum.

14. A propylene glycol solvate of a sodium salt of naproxen, which has peaks at 2-theta angles of approximately 6.7°, 9.7°, 15.8°, 18.6°, 20.8° and 22.8°, in a powder X-ray diffraction spectrum.

15. A method for preparing a propylene glycol solvate of a drug, which method comprises:

(a) contacting propylene glycol with a hygroscopic drug in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) isolating the solvate, wherein the drug is hygroscopic or has low aqueous solubility.

16. A method according to claim 15, wherein the step of crystallizing the solvate comprises changing the pH of the solution to precipitate the solvate.

17. A method according to claim 16, wherein the pH is raised to render the solution alkaline.

18. A method according to claim 15, wherein the step of isolating the solvate includes separating the solution phase from the solvate.

19. A method according to claim 18, wherein crystalline solvate is dried to remove excess solution phase.

20. A method for decreasing the hygroscopicity of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) isolating the solvate, wherein the solvate has decreased hygroscopicity as compared to the drug.

21. A method for increasing the aqueous solubility of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) isolating the solvate, wherein the solvate has increased aqueous solubility as compared to the drug.

22. A method according to claim 15, wherein the solvate has a powder X-ray diffraction spectrum which differs from the corresponding powder X-ray diffraction spectrum of the unsolvated drug by at least one property selected from

(i) a loss of at least one peak;

(ii) shifting of more than half the peaks at the 2-theta angle by at least 0.3°; and

(iii) formation of at least one new peak.

23. A method according to claim 15, wherein the solvate is stable to temperatures of up to 50°C under a stream of gas in a thermogravimetric analysis apparatus.

24. A method according to claim 15, wherein the drug is in the form of a metal salt.

25. A method according to claim 24, wherein the metal is an alkali metal or an alkaline earth metal.

26. A method according to claim 25, wherein the metal is selected from Na, K, Li, Ca and Mg.

27. A method according to claim 1, wherein the drug comprises . Celecoxib, Naproxen, Methyl prednisolone succinate ester, Impinem/Cilastatin, Fomivirsen sodium, Cerivastatin sodium, Dalfopristin/Quinopristin, Gonadorelin HCl(decapeptide), Clindamycin phosphate (ester prodrug), Famciclovir, Cyanocobalamin, Tolcapone, Epirubicin HCl, Colestipol HCl (anion exc.), Penicillin G potassium, Bacitracin (peptide), Fluvastatin sodium, Diclofenac sodium, Pilocarpine HCl, Bethanechol chloride, Trientine 2 (CH1), Montelukast sodium, Mechlorethamine HCl, Hydrocortisone phosphate ester, Dexamethasone phosphate ester, Chromolyn sodium,

Pyridostigmine bromide, Phentermine HCl, Telmisartan, Daunorubicin HCl, Praziquantel, and Pentosan polysulfate sodium.

28. A method according to claim 1, wherein the drug comprises has low aqueous solubility and is selected from the group consisting of steroid drugs.

Abstract

Pharmaceutical Compositions

A pharmaceutical composition comprising a propylene glycol solvate of a drug which is hygroscopic or which has low aqueous solubility.

FIG. 1

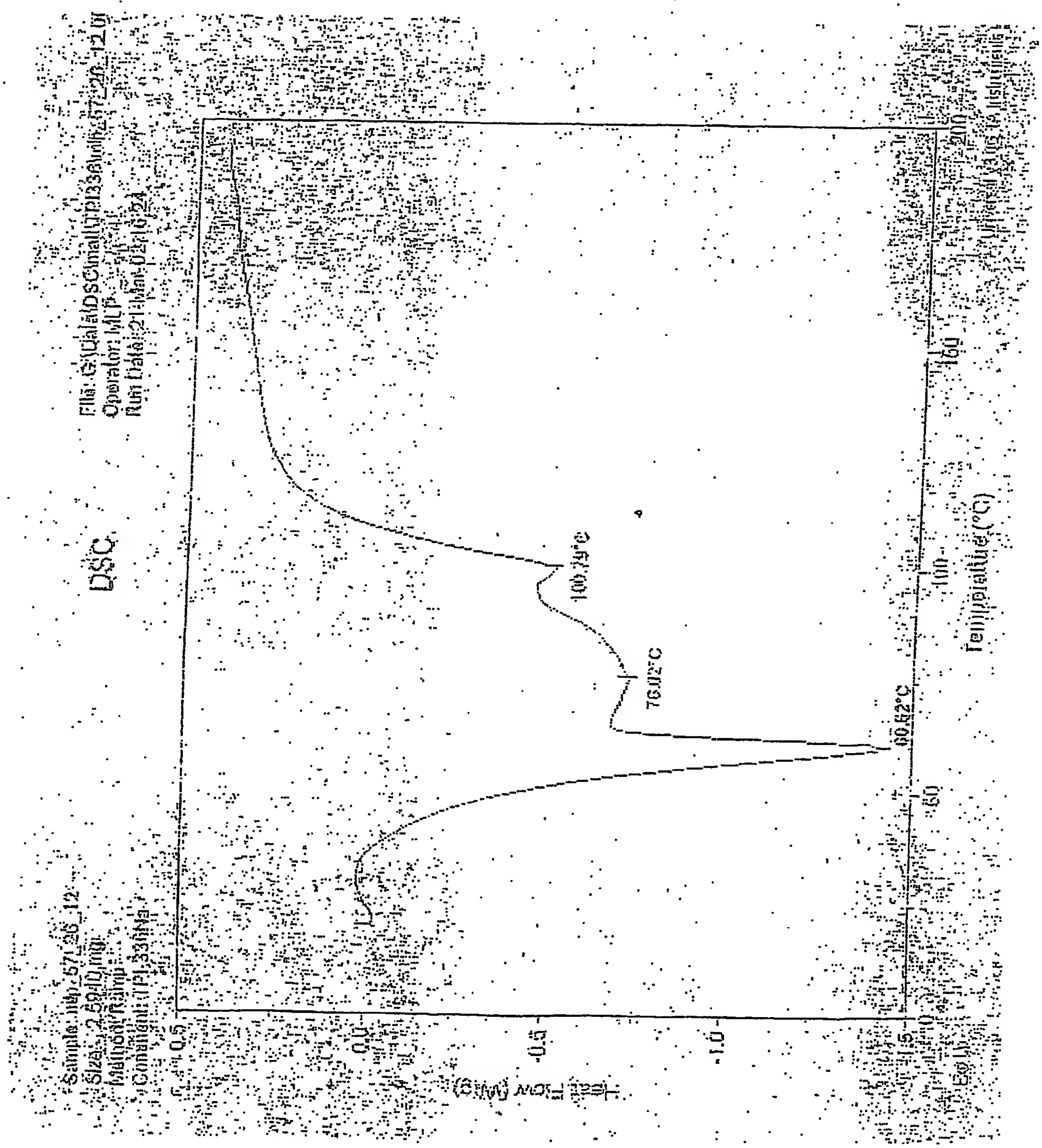
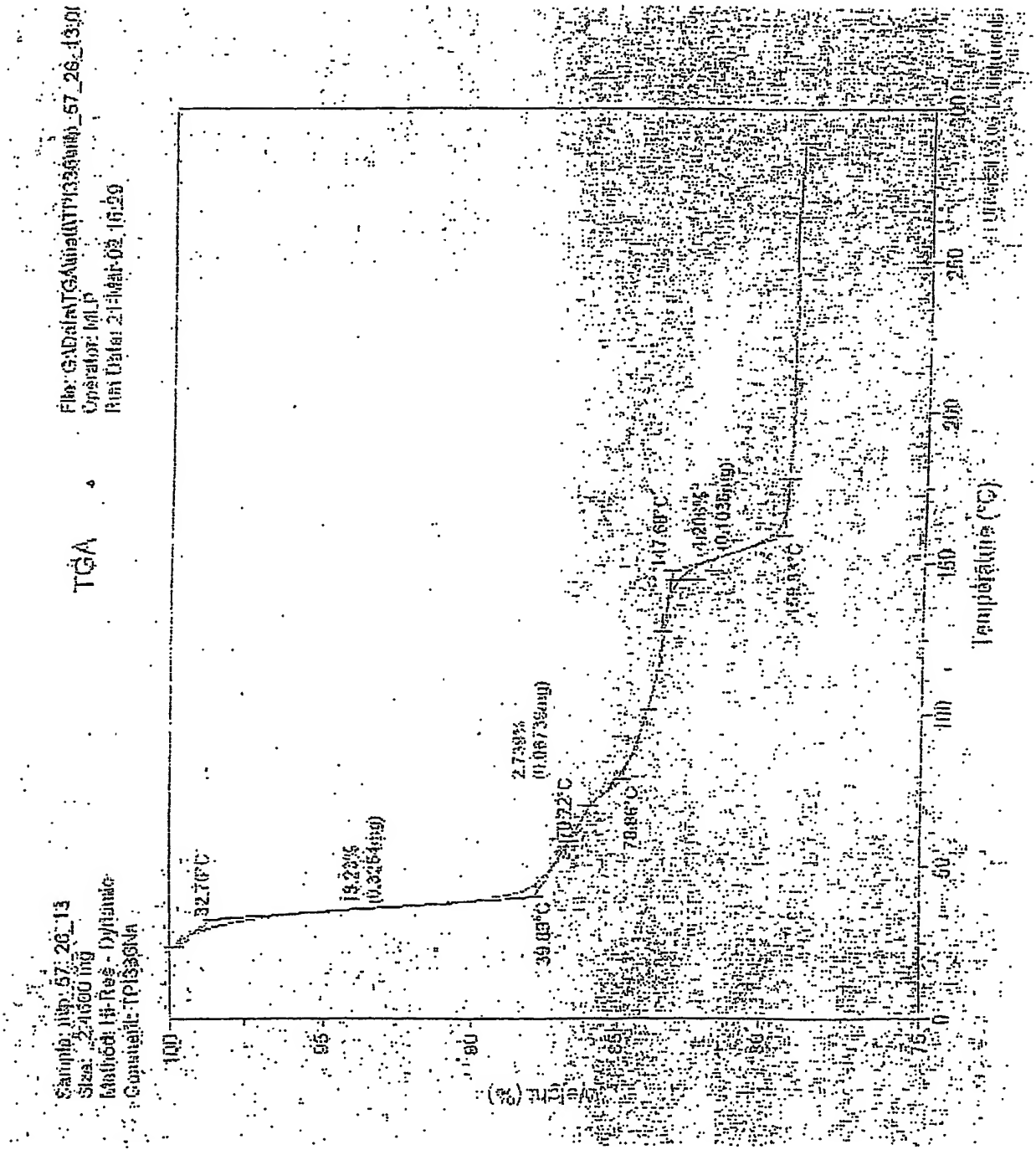


FIG. 2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Operator: MLP
Run Date: 21-Mar-02 16:29
Universal V3.0G TA Instruments
Weight (%)
Temperature (°C)
100
95
90
85
80
75
0
50
100
150
200
250
32.70°C
19.23%
(0.32464mg)
39.08°C
70.22°C
2.79%
(0.06736mg)
70.86°C
147.60°C
4.20%
(0.10136mg)

FIG. 3

Transform Pharmaceuticals, Inc.
Intensity(Counts)
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0
10
20
30
40
1500
1000
500

FIG. 4

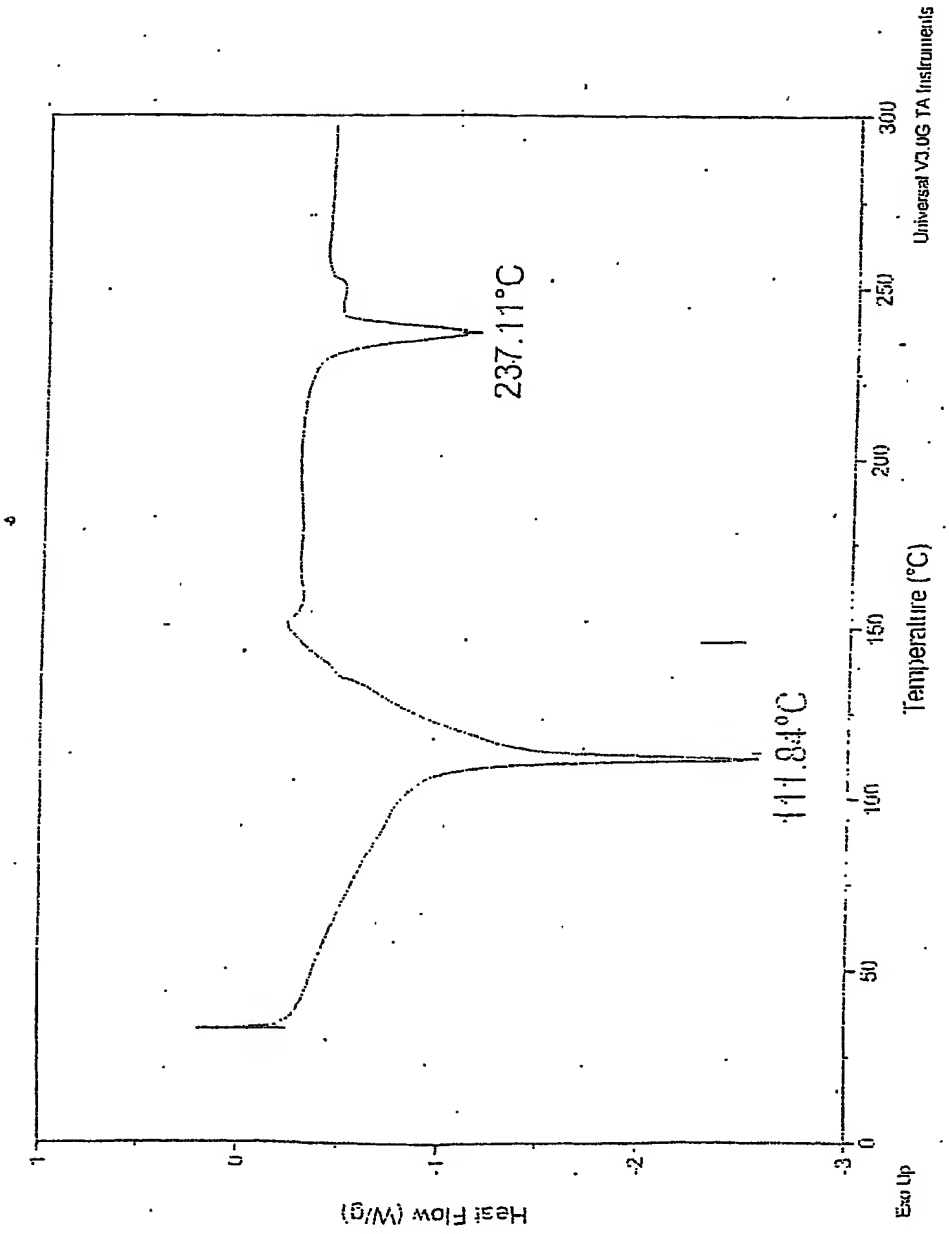
237.11°C
111.84°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V3.0G TA Instruments

FIG. 5

Weight (%)
105
100
95
90
85
80
Temperature (°C)
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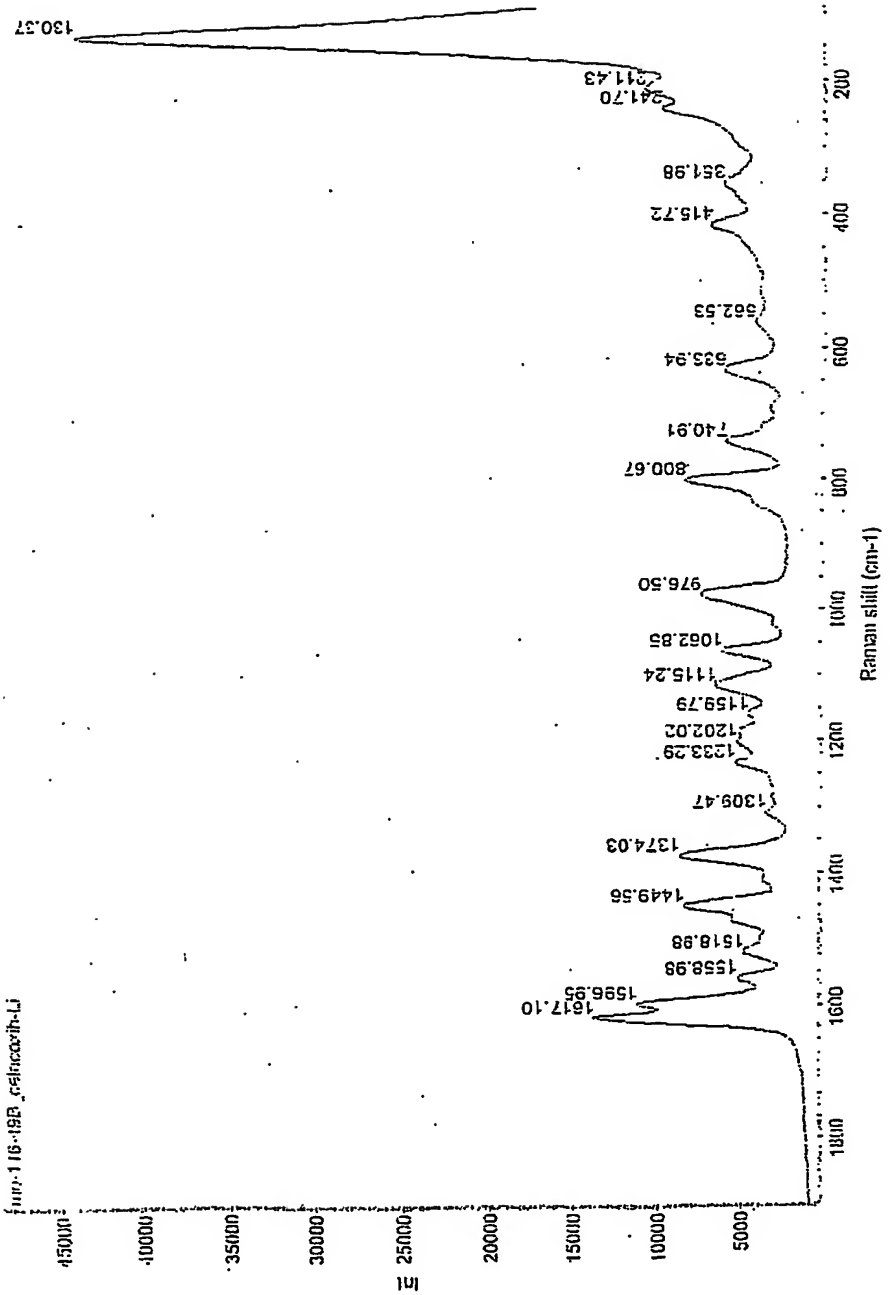
50
100
150
200
250
300
Universal V3.0G TA Instruments
14.00%,
(1.152mg)

FIG. 6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1202.02
1233.29
1309.47
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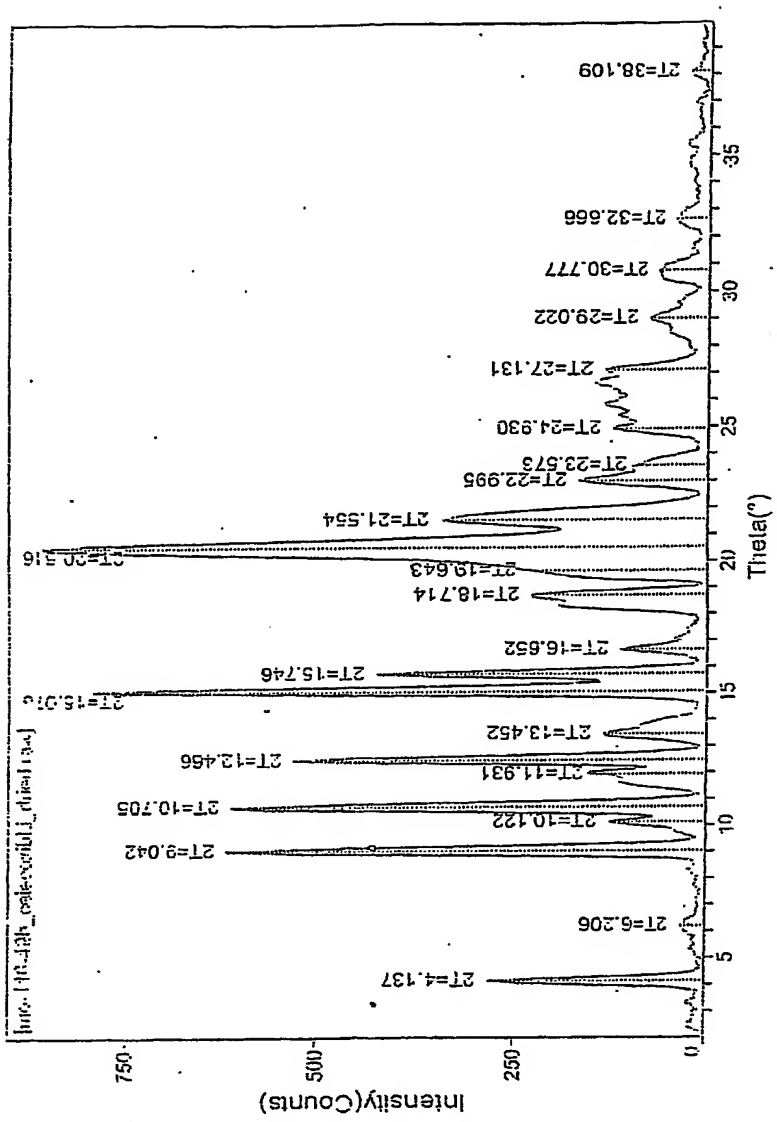
1558.98
1596.95
1617.10
Raman shift (cm-1)
Int.

FIG. 7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15
20
25
30
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2T=9.042
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2T=12.456
2T=13.452
2T=15.746
2T=16.652
2T=18.714
2T=19.643
2T=21.554
2T=22.995
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FIG. 8

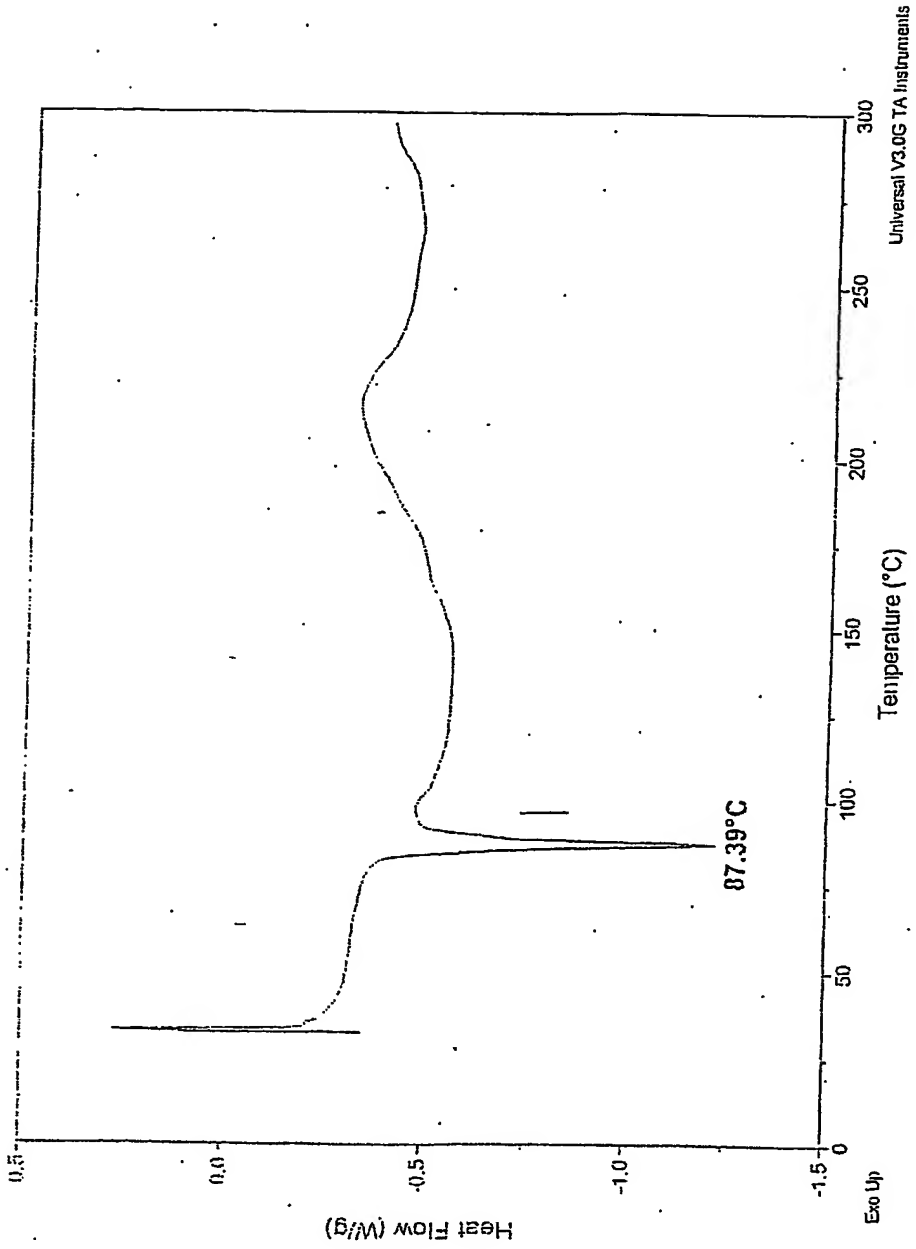


FIG. 9

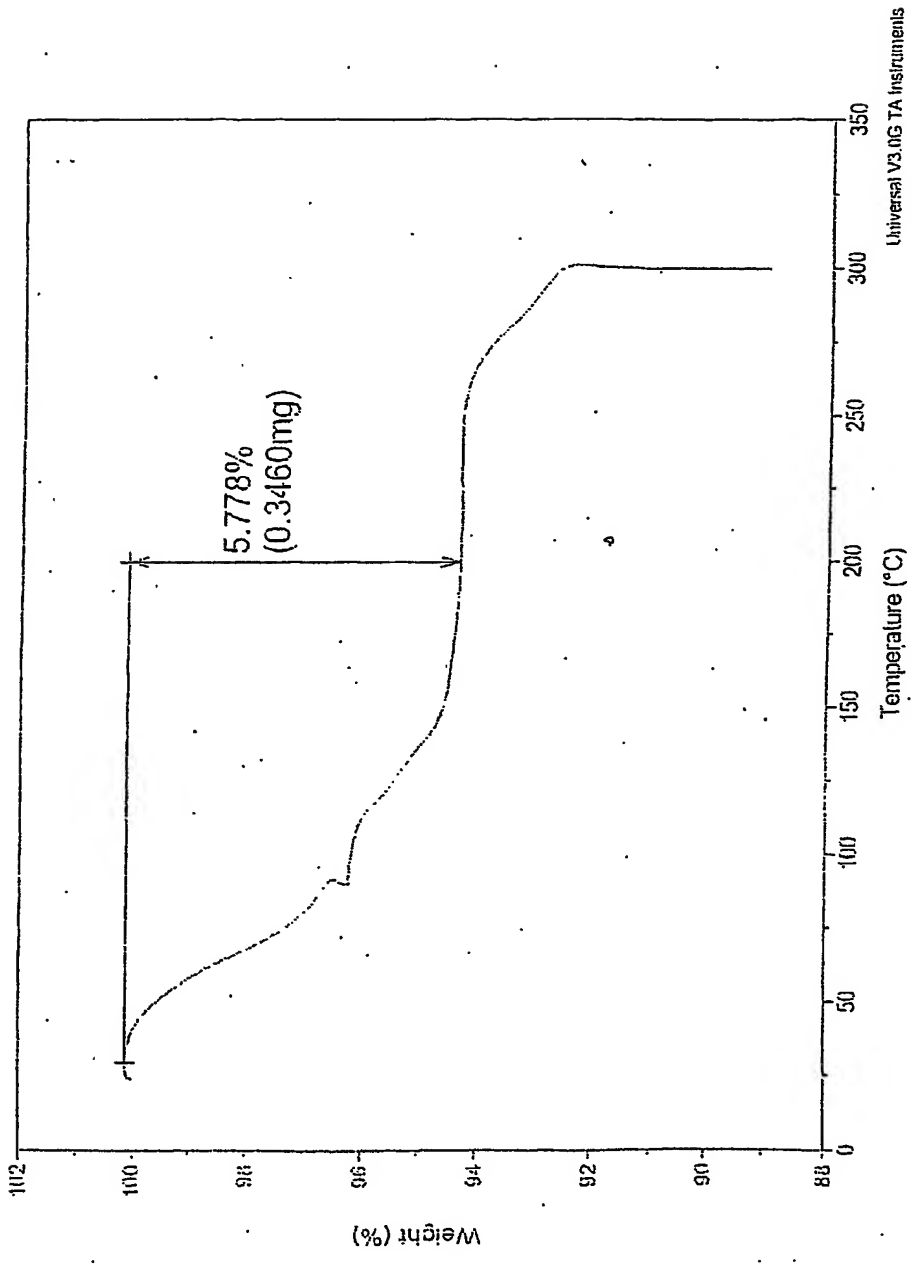
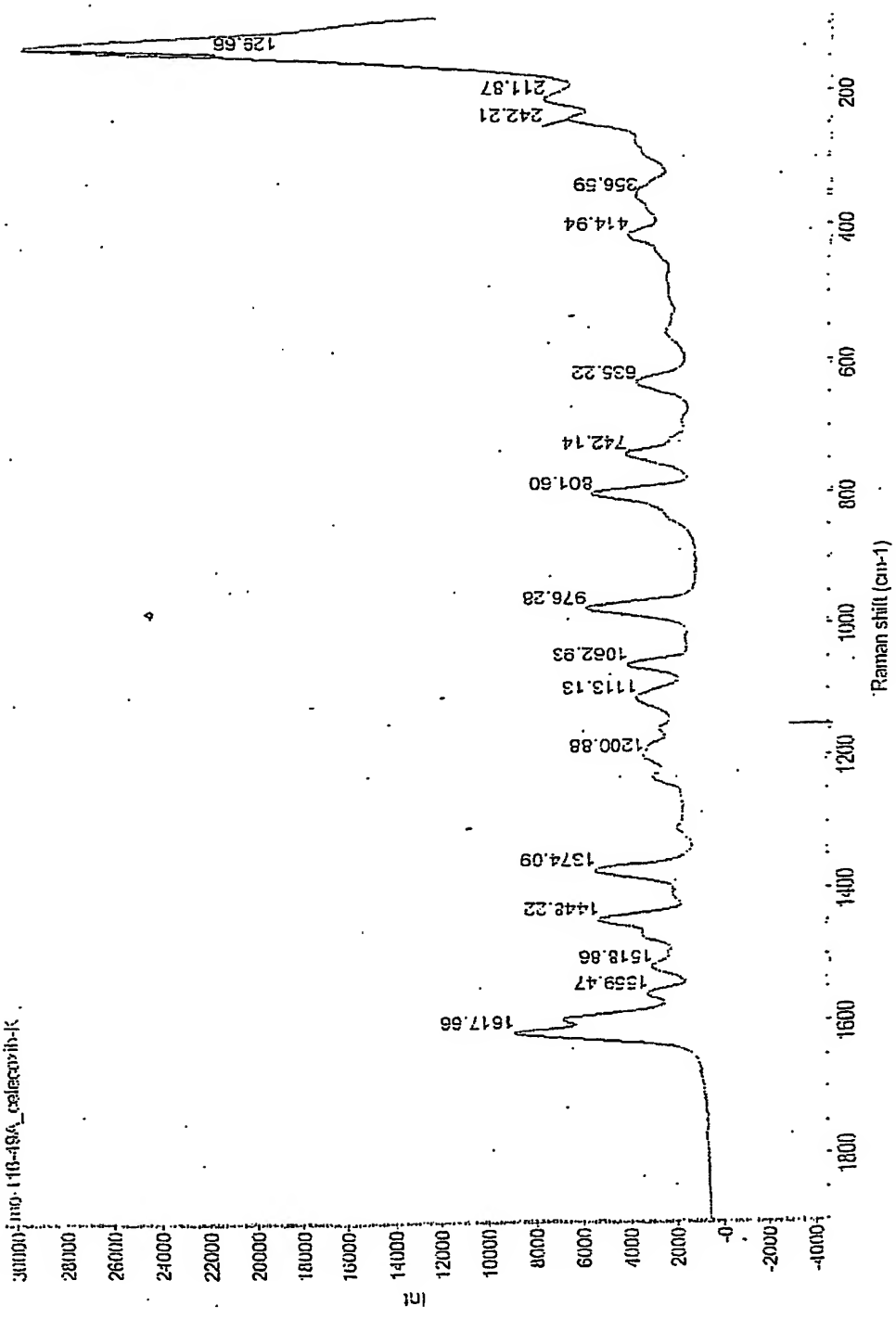

5.778%
(0.3460mg)
Weight (%)
Temperature (°C)
Universal V3.0G TA Instruments

FIG. 10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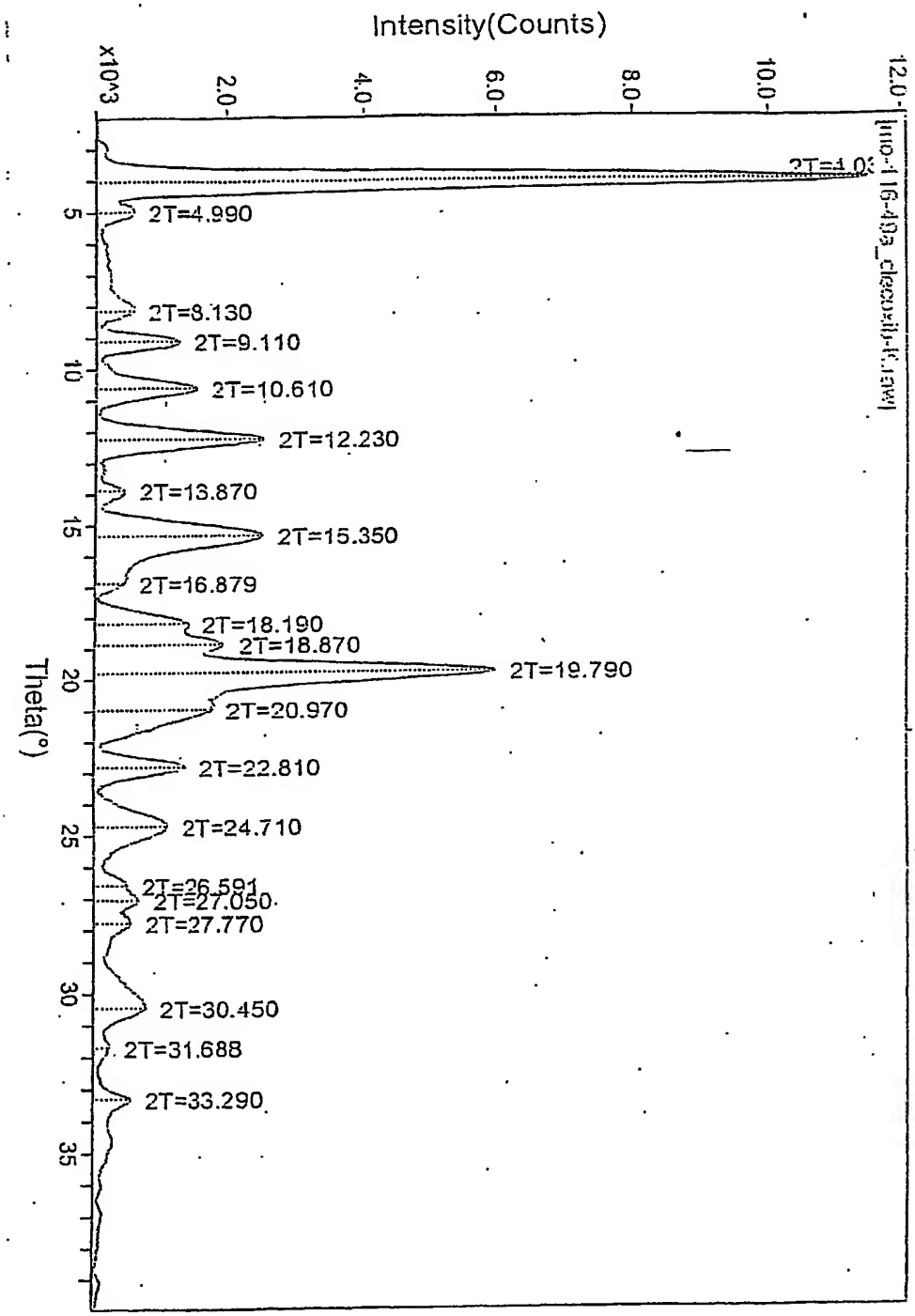
1559.47
1617.66
Raman shift (cm-1)
Int.


Intensity(Counts)
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4.0
6.0
8.0
10.0
12.0
Theta(°)
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10
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30
35
2T=4.990
2T=8.130
2T=9.110
2T=10.610
2T=12.230
2T=13.870
2T=15.350
2T=16.879
2T=18.190
2T=18.870
2T=19.790
2T=20.970
2T=22.810
2T=24.710
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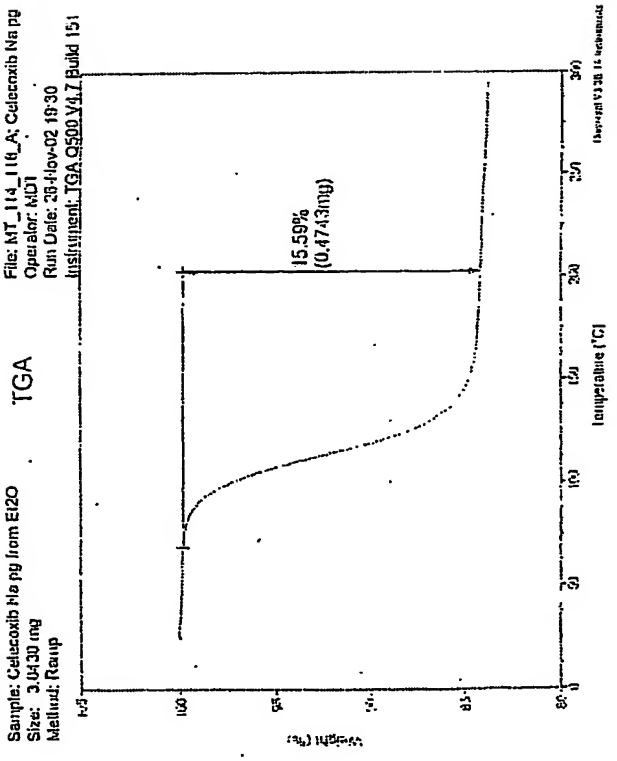
2T=31.688
2T=33.290

FIG. 11

FIG. 12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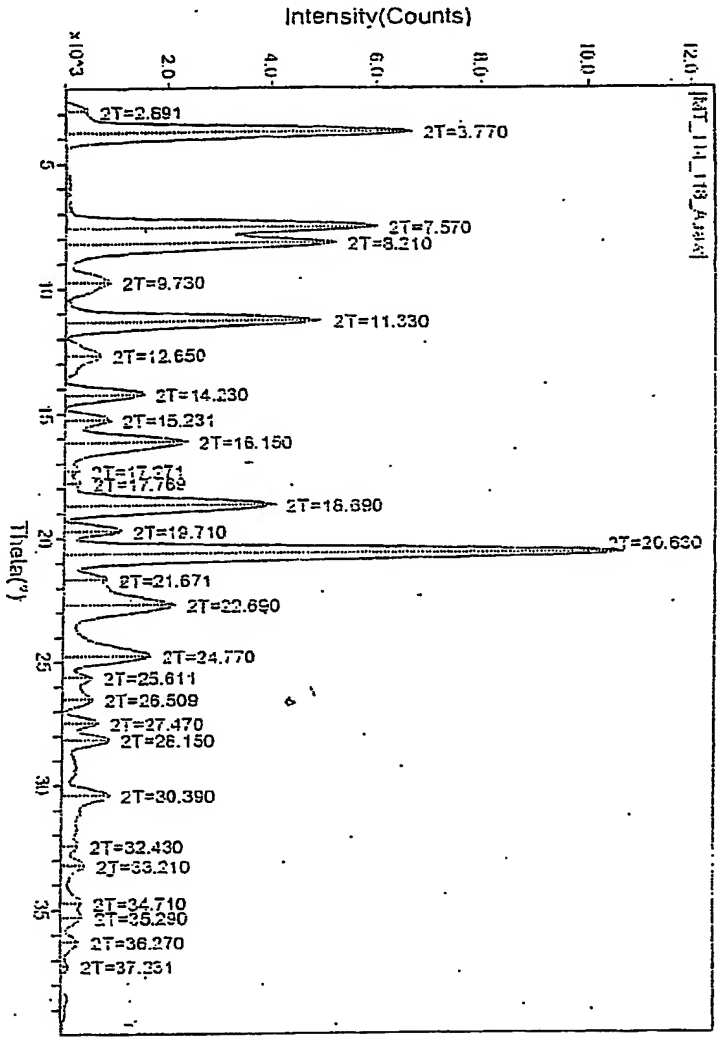
Size: 3.0430 mg
Method: Ramp
TGA
File: MT_114_116_A: Celecoxib Na pg
Operator: MDI
Run Date: 25-Nov-02 19:30
Instrument: TGA Q500 V4.7 Build 151
15.59%
(0.4743mg)
Temperature (°C)


Intensity(Counts)
×10^3
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4.0
6.0
8.0
10.0
12.0
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2T=3.770
2T=7.570
2T=8.210
2T=9.730
2T=11.330
2T=12.650
2T=14.230
2T=15.231
2T=16.150
2T=17.271
2T=17.769
2T=18.690
2T=19.710
2T=20.630
2T=21.671
2T=22.690
2T=24.770
2T=25.611
2T=26.509
2T=27.470
2T=28.150
2T=30.390
2T=32.430
2T=33.210
2T=34.710
2T=35.290
2T=36.270
2T=37.231
Theta(°)
5
10
15
20
25
30
35

FIG. 13

FIG. 14

FIG. 15

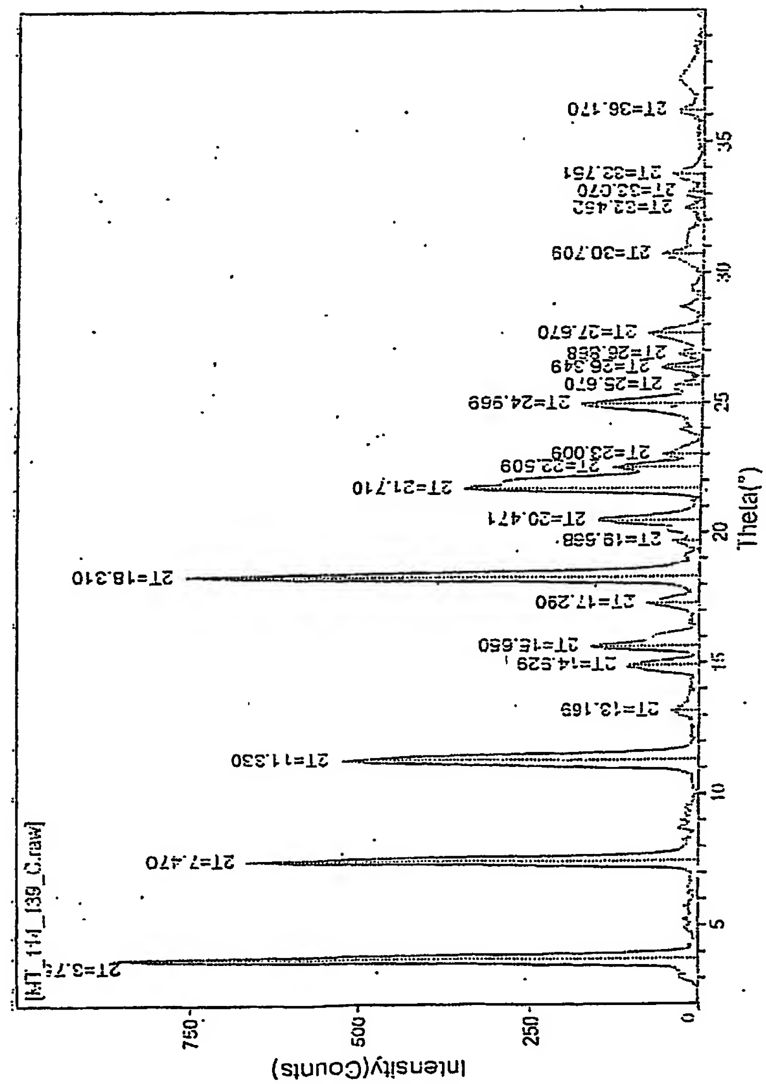
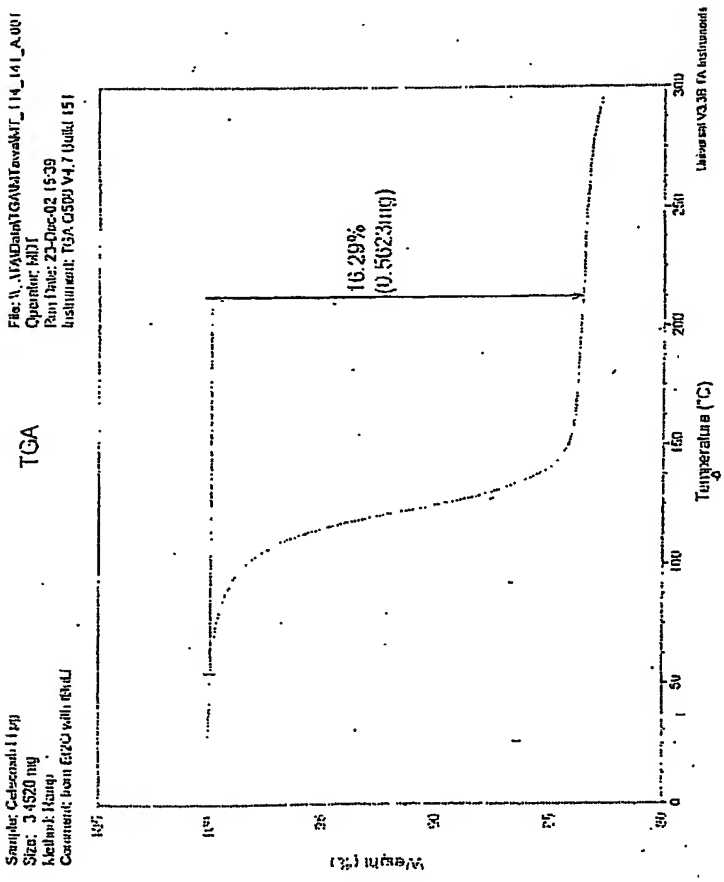

2T=7.470
2T=11.330
2T=13.169
2T=14.529
2T=15.650
2T=17.290
2T=18.310
2T=20.471
2T=21.710
2T=22.509
2T=23.009
2T=24.969
2T=25.670
2T=26.349
2T=27.670
2T=30.709
2T=32.452
2T=33.070
2T=33.751
2T=36.170
Theta(°)
Intensity(Counts)
0
250
500
750
5
10
15
20
25
30
35

FIG. 16


TGA
16.29%
(0.5623mg)
Weight (%)
Temperature (°C)
Universal V4.3B TA Instruments

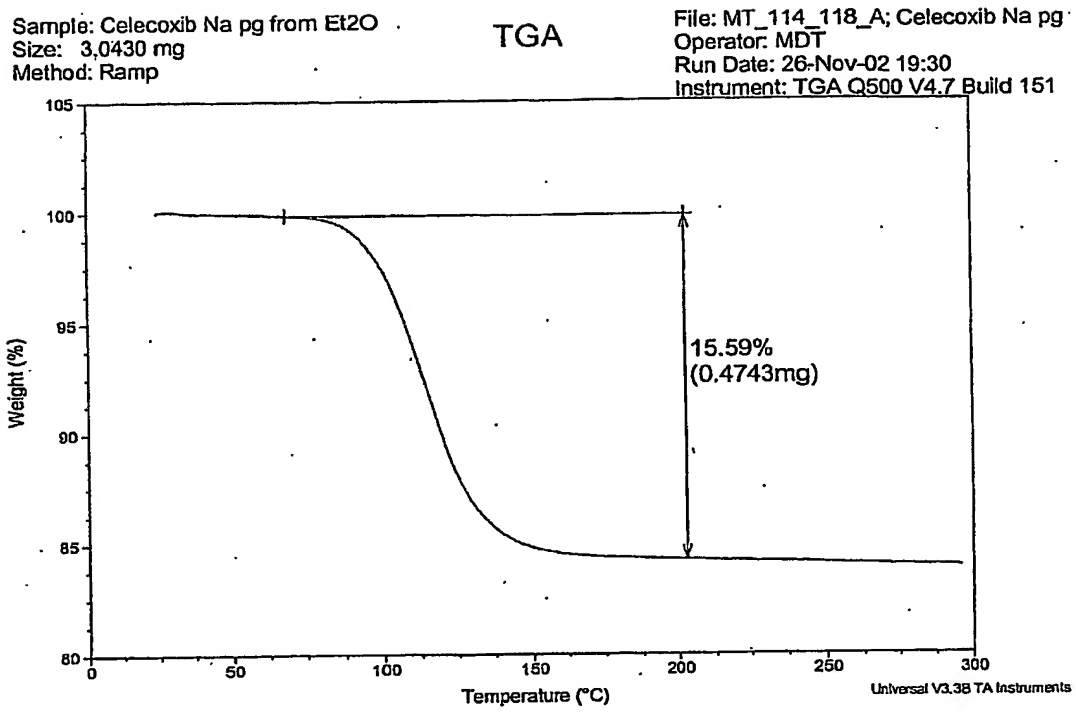

Sample: Celecoxib Na pg from Et2O
Size: 3,0430 mg
Method: Ramp
TGA
File: MT_114_118_A; Celecoxib Na pg
Operator: MDT
Run Date: 26-Nov-02 19:30
Instrument: TGA Q500 V4.7 Build 151
105
100
95
90
85
80
Weight (%)
15.59%
(0.4743mg)
0
50
100
150
200
250
300
Temperature (°C)
Universal V3.38 TA Instruments

Fig. 17

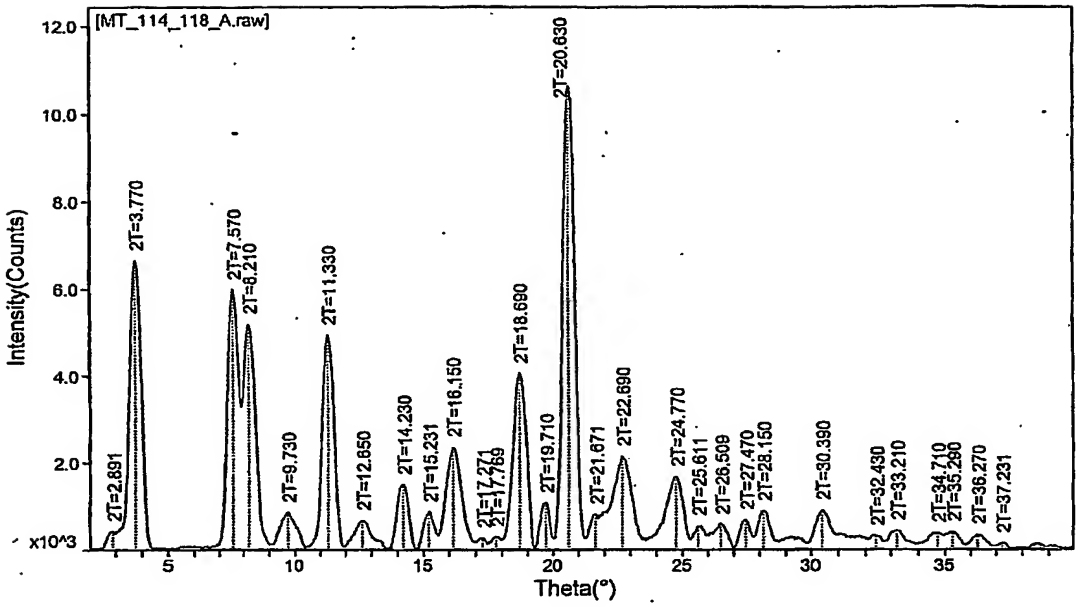

[MT_114_118_A.raw]
Intensity(Counts)
x10^3
Theta(°)
2T=2.891
2T=3.770
2T=7.570
2T=8.210
2T=9.730
2T=11.330
2T=12.650
2T=14.230
2T=15.231
2T=16.150
2T=17.271
2T=17.769
2T=18.690
2T=19.710
2T=20.630
2T=21.671
2T=22.690
2T=24.770
2T=25.611
2T=26.509
2T=27.470
2T=28.150
2T=30.390
2T=32.430
2T=33.210
2T=34.710
2T=35.290
2T=36.270
2T=37.231

Fig. 18

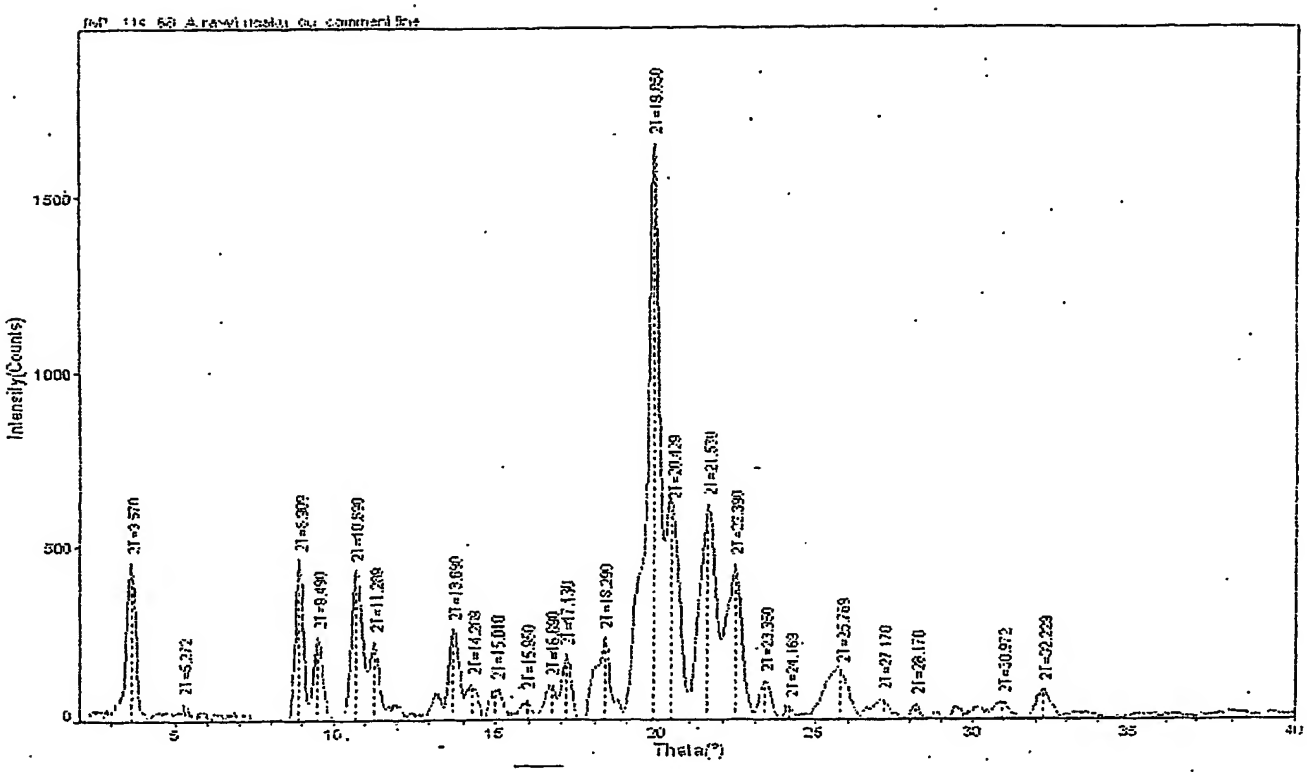

Intensity(Counts)
1500
1000
500
0
Theta(°)
2T=5.272
2T=6.909
2T=8.490
2T=10.890
2T=11.209
2T=13.690
2T=14.209
2T=15.010
2T=15.950
2T=16.690
2T=17.130
2T=18.290
2T=19.850
2T=20.439
2T=21.570
2T=23.390
2T=23.950
2T=24.169
2T=25.769
2T=27.170
2T=28.170
2T=30.972
2T=32.229

FIG. 19A

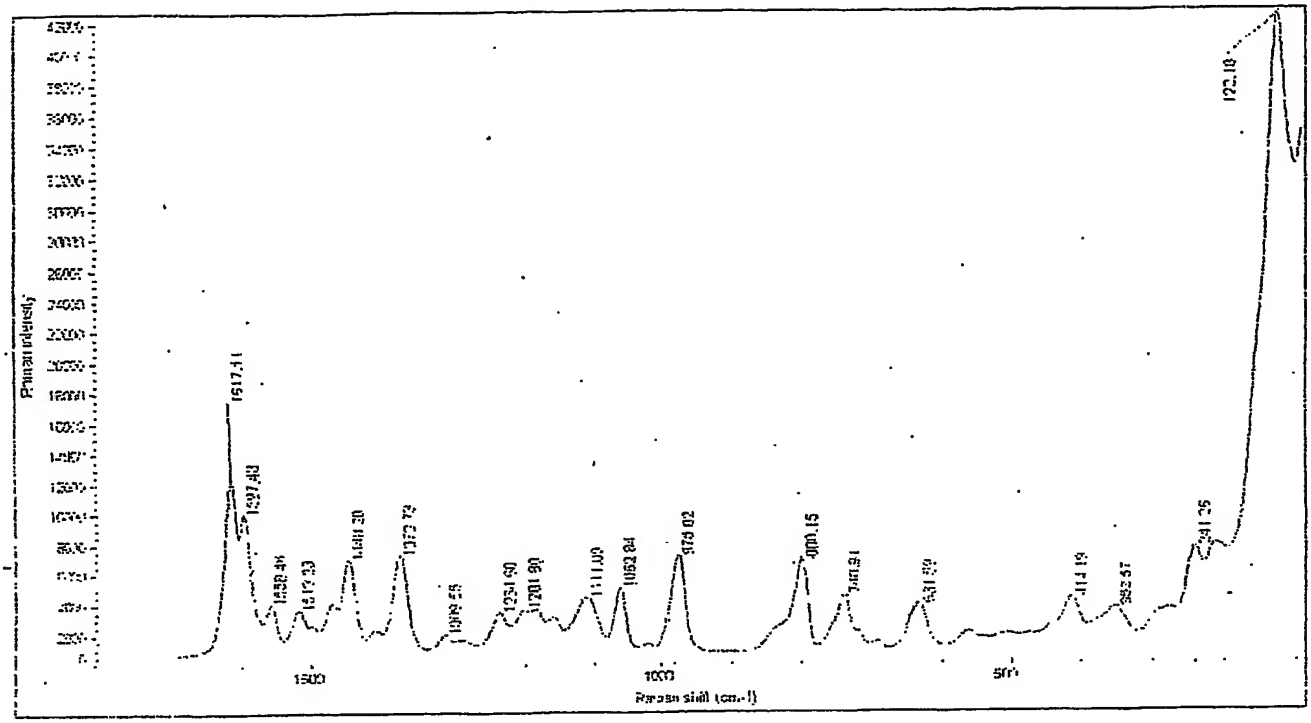

Raman intensity
1617.11
1597.48
1438.46
1372.72
1251.60
1201.80
1111.00
1052.84
973.02
900.15
841.91
761.89
711.19
382.57
122.18
1500
1000
500
Raman shift (cm-1)

FIG. 19B

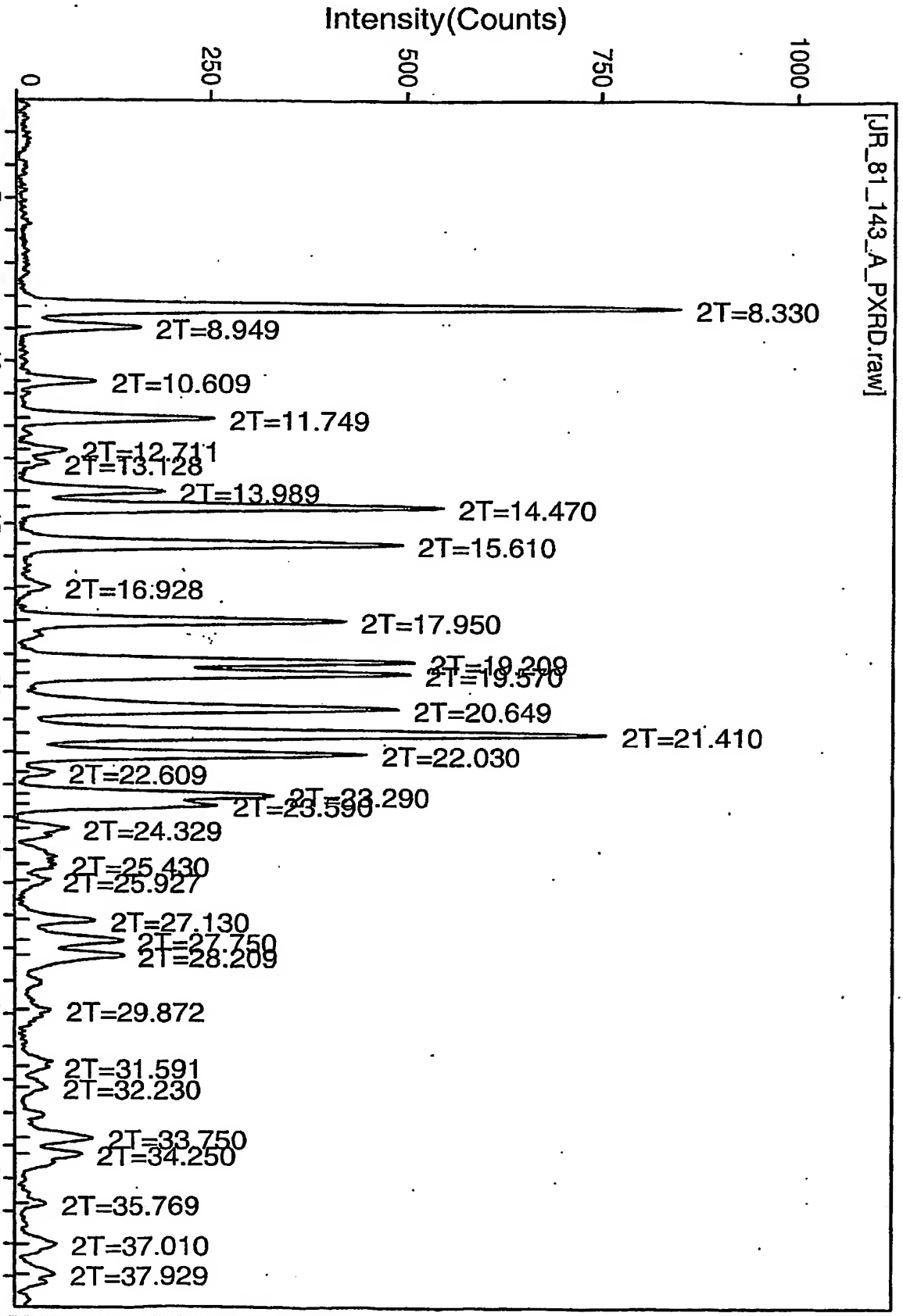

Intensity(Counts)
0
250
500
750
1000
[JR_81_143_A_PXRD.raw]
Theta(°)
5
10
15
20
25
30
35
2T=8.330
2T=8.949
2T=10.609
2T=11.749
2T=12.711
2T=13.128
2T=13.989
2T=14.470
2T=15.610
2T=16.928
2T=17.950
2T=19.209
2T=19.570
2T=20.649
2T=21.410
2T=22.030
2T=22.609
2T=23.290
2T=23.590
2T=24.329
2T=25.430
2T=25.927
2T=27.130
2T=27.750
2T=28.209
2T=29.872
2T=31.591
2T=32.230
2T=33.750
2T=34.250
2T=35.769
2T=37.010
2T=37.929

Fig. 79A

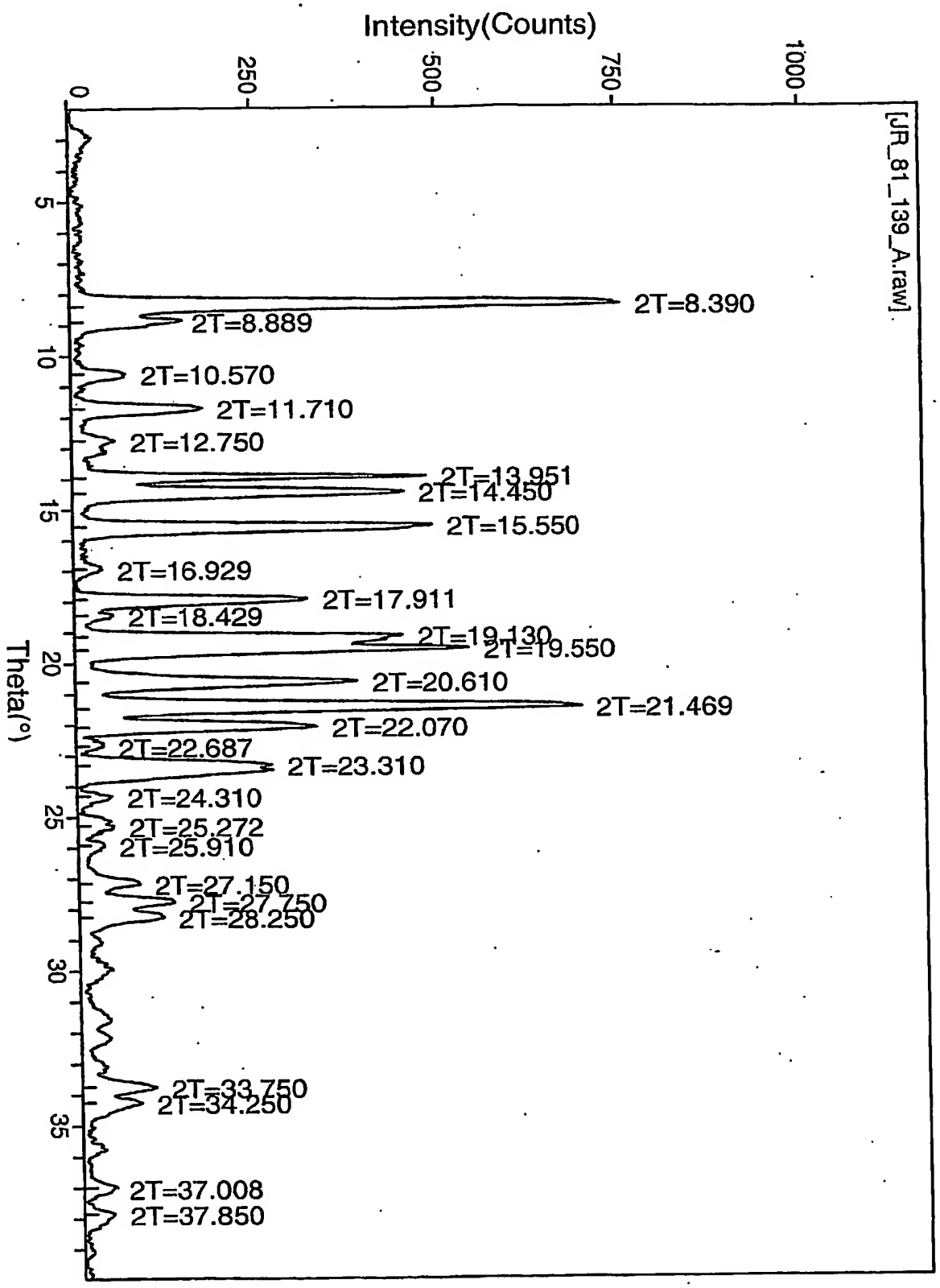


Fig 208

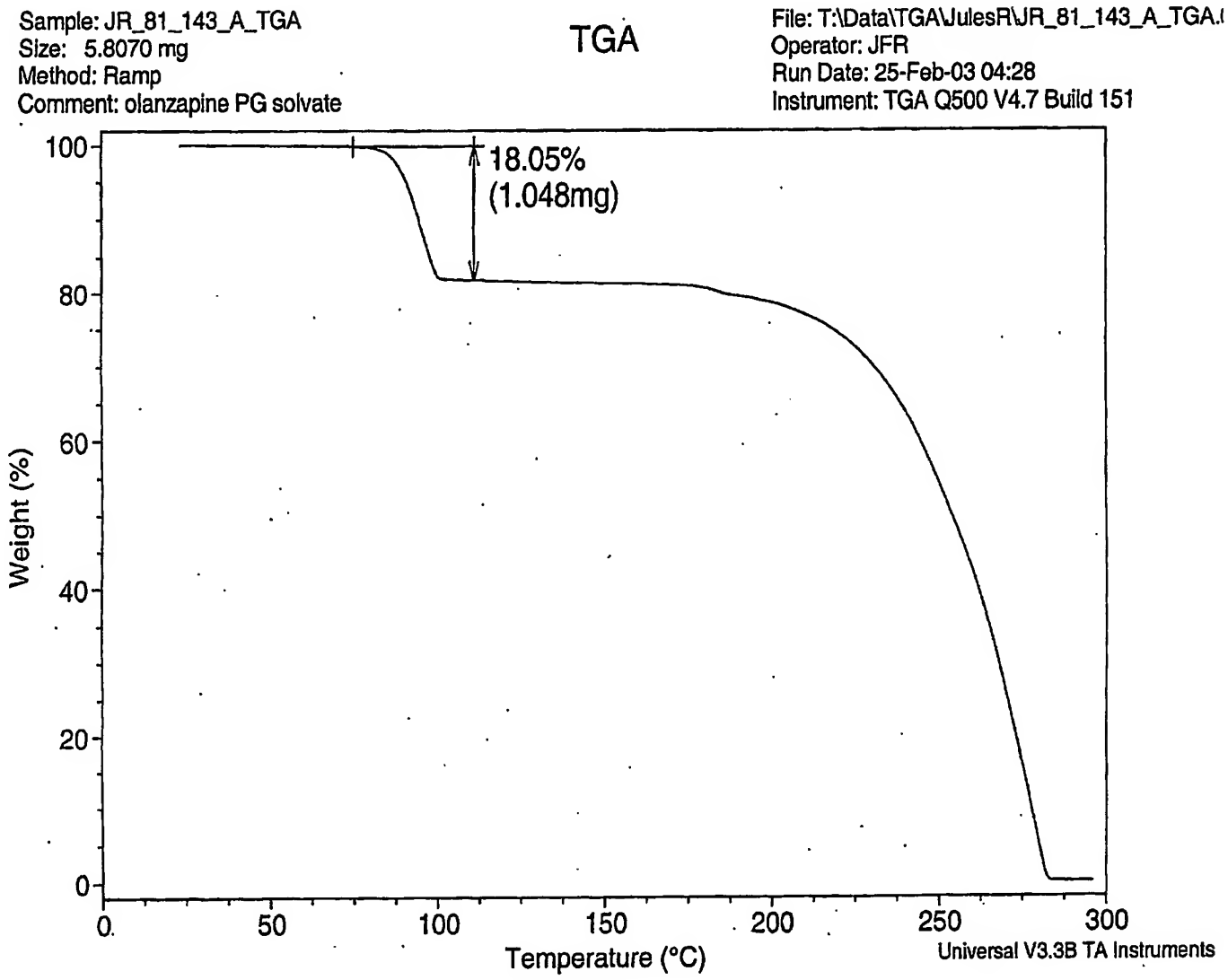


Fig 21

Sample: JR_81_143_A_DSC
Size: 2.2280 mg
Method: Ramp

DSC

File: T:\Data\DSC\JulesR\JR_81_143_A_DSC.
Operator: JFR
Run Date: 25-Feb-03 04:14
Instrument: DSC Q1000 V6.19 Build 227

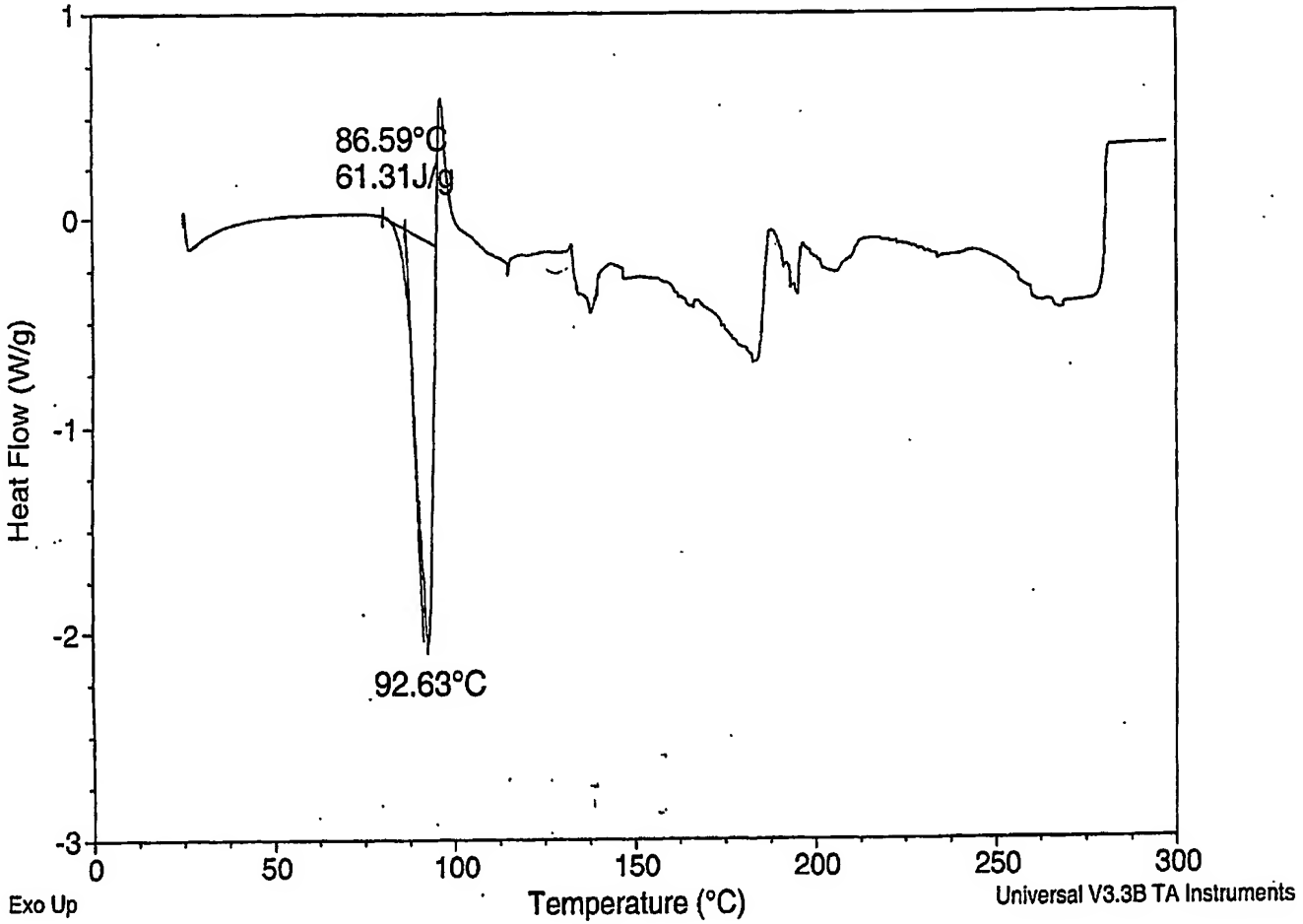


Fig 22

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